University of Alberta

A grip on the functional impacts of carpal tunnel syndrome and its therapeutic interventions

by

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Dedication

I dedicate this thesis to my parents, who have helped me to achieve my goals by their continuing support, love and encouragement.

Abstract

In a search for hand function tests that engage the median innervated territory of the hand, we identified the Moberg Pick-Up Test as a potentially suitable tool. The first project was to establish norms for the Moberg Pick-Up Test. It showed that age, gender, and handedness affect the manual dexterity of healthy subjects. Older age, male gender and using the non-dominant hand compromised hand function performance.

Although functional impairment of hands is a common consequence of CTS, there were no valid and reliable tools available to quantify the hand disability in these patients. The second project was aimed at establishing valid and reliable hand function tests for CTS. Subjects were grouped by age as well as severity of CTS. The latter was determined based on the Levine's Self-Assessment Questionnaire and nerve conduction study results. It demonstrated a good correspondence between the severity of CTS and the functional impairment detected by the Purdue Pegboard Test and Moberg Pick-Up Test. There was a high correlation between the hand function scores on these two tests. Therefore both tools are suitable for this purpose and both had good test-retest reliability in CTS subjects.

The third project focused on enhancing axonal regeneration after carpal tunnel release surgery. In a randomized controlled trial, the effect of 1-hour, 20 Hz electrical stimulation of the median nerve after the decompression surgery on axonal regeneration was tested. Subjects were monitored at regular intervals for one year after the operation. Nerve conduction studies, the Purdue Pegboard Test, Levine's Self-Assessment Questionnaires, and Semmes Weinstein Monofilaments were used to

measure clinical outcome. We did motor unit number estimation (MUNE) to compare the number of regenerated motoneurons between the two groups. Compared to the control group, the stimulation group had a significant improvement in MUNE, detectable by 6-8 months after the surgery. Also, nerve conduction studies supported an accelerated improvement in the sensory and motor values in the stimulation group.

The last project examined the effectiveness of corticosteroid iontophoresis as a non-invasive treatment for CTS through a double blind randomized controlled trial. The same subjective and objective outcome measure tools as in the previous project were used to compare the effectiveness of 0.4% dexamethasone with placebo up to six months after the treatment. There was no significant difference in any of the outcome measures between the treatment and control group. Therefore, we conclude that iontophoresis of 0.4% dexamethasone is ineffective in treating CTS.

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Table of Contents

1.0: General Introduction *1*

1.1: NERVE COMPRESSION WITHIN THE CARPAL TUNNEL *2*

1.1.1: Anatomy of the Carpal Tunnel *2*

1.1.2: Carpal Tunnel Contents and Pressure *3*

1.1.3: Median Innervation of the Hand *4*

1.1.4: Manifestations of Carpal Tunnel Syndrome *6*

1.1.5: Electrodiagnosis of CTS *8*

1.2: PATHOPHYSIOLOGY OF THE MEDIAN NERVE COMPRESSION *10*

1.2.1: The Median Nerve *10*

1.2.2: Nerve Fibers *11*

1.2.3: Axoplasmic Transport *11*

1.2.4: Nerve Response to Compression Injury *12*

1.2.4.1: Mild/Acute Nerve Compression *12*

1.2.4.2: Severe/Chronic Nerve Compression *13*

1.2.5: Classification of Nerve Injury *14*

1.2.6: Nerve Regeneration in Crushed Nerves *15*

1.3: OBJECTIVES OF THE THESIS *16*

REFERENCE LIST *18*

2.0: Normative Values and the Effects of Age, Gender and Handedness on the Moberg Pick-Up Test *29*

2.1: INTRODUCTION *30*

2.2: METHODS........31

2.2.1: Subjects........31

2.2.2: The Moberg Pick-Up Test........32

2.2.3: Statistical Analysis........33

2.3: RESULTS........33

2.4: DISCUSSION........35

REFERENCE LIST........38

3.0: Validity and Reliability of the Purdue Pegboard Test and the Moberg Pick-Up Test in Patients with Carpal Tunnel Syndrome........47

3.1: INTRODUCTION........48

3.2: METHODS........50

3.2.1: Healthy Subjects........50

3.2.2: CTS Subjects........50

3.2.3: Nerve Conduction Studies........51

3.2.3.1: Median Sensory Nerve Conduction Studies........51

3.2.3.2: Median Motor Nerve conduction Studies........52

3.2.4: Levine's Self-Assessment Questionnaire for CTS........52

3.2.5: The Purdue Pegboard Test........53

3.2.6: The Moberg Pick-Up Test........54

3.2.7: Statistical Analysis........55

3.3: RESULTS........56

3.3.1: Subjects........56

3.3.2: The Purdue Pegboard Test *57*

3.3.2.1: Severity of CTS Based on NCS *57*

3.3.2.2: Severity of CTS Based on Levine's Self-Assessment Questionnaire for CTS Score *58*

3.3.3: The Moberg Pick-Up Test *59*

3.3.3.1: Severity of CTS based on NCS *59*

3.3.3.2: Severity of CTS based on Levine's Self-Assessment Questionnaire for CTS Score *61*

3.3.4: Test-Retest Reliability *63*

3.3.5: Correlations *63*

3.4: DISCUSSION *63*

REFERENCE LIST *67*

4.0: Electrical Stimulation after Decompression Surgery Promotes Nerve Regeneration in Carpal Tunnel Syndrome *81*

4.1: INTRODUCTION *82*

4.2: METHODS *84*

4.2.1: Subjects *84*

4.2.2: Nerve Conduction Study *85*

4.2.2.1: Median Sensory Nerve Conduction Study *85*

4.2.2.2: Median Motor Nerve Conduction Study *86*

4.2.3: Treatment Protocol *87*

4.2.3.1: Surgical Technique *87*

4.2.3.2: Electrical Stimulation *88*

4.2.4: Outcome Measures *89*

4.2.4.1: Nerve Conduction Studies *89*

4.2.4.2: Motor Unit Number Estimation (MUNE) *90*

4.2.4.3: Levine's Self-Assessment Questionnaire for CTS *91*

4.2.4.4: The Purdue Pegboard Test *92*

4.2.4.5: Semmes Weinstein Monofilaments (SWM) *93*

4.2.5: Statistical Analysis *93*

4.3: RESULTS *94*

4.3.1: Subjects *94*

4.3.2: Outcomes *95*

4.3.2.1: Nerve Conduction Studies *95*

4.3.2.2: Motor Unit Number Estimation *97*

4.3.2.3: Levine's Self-Assessment Questionnaire *98*

4.3.2.4: The Purdue Pegboard Test *98*

4.3.2.5: Semmes Weinstein Monofilaments *99*

4.4: DISCUSSION: *100*

REFERENCE LIST *105*

5.0: Corticosteroid Iontophoresis is not an Effective Treatment for Carpal tunnel Syndrome *118*

5.1: INTRODUCTION *119*

5.2: METHODS *121*

5.2.1: Subjects *121*

5.2.2: Nerve Conduction Study *122*

5.2.2.1: Median Sensory Nerve Conduction Study *122*

5.2.2.2: Median Motor Nerve Conduction Study *122*

5.2.3: Motor Unit Number Estimation (MUNE) *123*

5.2.4: Treatment Protocol *125*

5.2.5: Outcome Measure Tools *126*

5.2.5.1: Nerve Conduction Studies *126*

5.2.5.2: Levine's Self-Assessment Questionnaire for CTS *127*

5.2.5.3: The Purdue Pegboard Test *127*

5.2.5.4: Semmes Weinstein Monofilaments (SWM) *128*

5.2.6: Statistical Analysis *129*

5.3: RESULTS *129*

5.3.1: Subjects *129*

5.3.2: Outcomes *130*

5.3.2.1: Nerve Conduction Studies *130*

5.3.2.2: Levine's Self-Assessment Questionnaire *131*

5.3.2.3: The Purdue pegboard Test *131*

5.3.2.4: Semmes Weinstein Monofilaments *132*

5.4: DISCUSSION *132*

REFERENCE LIST *136*

6.0: General Discussion and Future Directions *147*

6.1: PROJECT 1: ESTABLISHMENT OF NORMS FOR THE MOBERG PICK-UP TEST 147

6.2: PROJECT 2: VALIDITY AND RELIABILITY OF THE PURDUE-PEGBOARD TEST AND THE MOBERG PICK-UP TEST 149

6.3: PROJECT 3: ENHANCEMENT OF AXONAL REGENERATION AFTER DECOMPRESSION OF THE MEDIAN NERVE BY USING ELECTRICAL STIMULATION 150

6.4: PROJECT 4: INEFFECTIVENESS OF CORTICOSTEROID IONTOPHORESIS IN TREATING MILD AND MODERATE CTS 152

6.5: CONCLUDING REMARKS 154

6.6: REFERENCE LIST 155

Appendix 1 159

List of Tables

Table 2.1. *Normative values for the Moberg pick-Up Test based on the age and gender of subjects.*

Table 3.1. *Comparison of CTS severity based on NCS criteria and Levine's Self-Assessment Questionnaire for CTS scores.*

List of Figures

Figure 1.1. *Anatomy of the carpal tunnel.*

Figure 1.2. *Median innervation territory at the palm.*

Figure 2.1. *Presentation of the Moberg Pick-Up Test.*

Figure 2.2. *Impact of the age of subjects on performing the Moberg Pick-Up Test with eyes open.*

Figure 2.3. *Impact of the age of subjects on performing the Moberg Pick-Up Test with eyes closed.*

Figure 2.4. *Impact of the gender of subjects on performing the Moberg Pick-Up Test with eyes open.*

Figure 2.5. *Impact of gender of subjects on performing the Moberg Pick-Up Test with eyes closed.*

Figure 2.6. *Comparison of the skillfulness of the dominant and non dominant hand in executing the Moberg Pick-Up Test.*

Figure 3.1. *Distribution of CTS and control subjects in the three age groups.*

Figure 3.2. *Performance of CTS subjects on the Purdue Pegboard Test: severity based on nerve conduction studies.*

Figure 3.3. *Performance of CTS subjects on the Purdue Pegboard Test: severity based on Levine's Self-Assessment Questionnaire.*

Figure 3.4. *Performance of CTS subjects on the Moberg Pick-Up Test: CTS severity is based on nerve conduction studies.*

Figure 3.5. *Performance of CTS subjects on the Moberg Pick-Up Test: CTS severity is based on Levine's Self-Assessment Questionnaire.*

Figure 3.6. *Test-retest correlation of the Purdue Pegboard Test and the Moberg Pick-Up Test.*

Figure 3.7. *Correlation between the Purdue Pegboard Test and the Moberg Pick-Up Test.*

Figure 4.1. *Experiment set up.*

Figure 4.2. *Motor nerve conduction studies.*

Figure 4.3. *Sensory nerve conduction studies.*

Figure 4.4. *Comparison of MUNE in the stimulation and control group.*

Figure 4.5. *Comparison of Levine's Self Assessment Questionnaire.*

Figure 4.6. *Comparison of the Purdue Pegboard Test.*

Figure 4.7. *Comparison of Semmes Weinstein Monofilaments.*

Figure 5.1. *The experiment setup.*

Figure 5.2. *Results of motor nerve conduction studies.*

Figure 5.3. *Results of sensory nerve conduction studies.*

Figure 5.4. *Results of Levine's Self-Assessment Questionnaire.*

Figure 5.5. *Results of the Purdue Pegboard Test.*

Figure 5.6. *Results of Semmes Weinstein Monofilaments.*

Chapter 1

1.0 General Introduction:

Peripheral nerves are prone to various injuries such as compression, traction, laceration and severance. There are several anatomically constrained locations in the human body where the traversing nerves can be compressed within restricted boundaries, leading to entrapment neuropathies. Compression of the median nerve at the carpal tunnel, known as carpal tunnel syndrome (CTS), is by far the most common entrapment neuropathy [1]. Since the median nerve plays a major part in the motor and sensory innervation of the hand, its injury can cause severe functional impairment in the affected individuals.

Although CTS is not a life threatening condition, it poses a vast burden to industries as well as the healthcare system. It is particularly common among workers in occupations that require repetitive and strenuous manual labor [2-4]. Not surprisingly, it results in many workers compensation claims and reduction in productivity [5;6]. In the 1988 US National Health Interview Survey, 2.65 million of the 170 million adult respondents living in the United States had symptoms of carpal tunnel syndrome [7]. In Alberta alone, the compensation paid by the Workers' Compensation Board between 1999 and 2001 was almost $20 million for the repetitive stress injury to the wrist of which carpal tunnel syndrome forms a major portion (based on claims data from the Alberta Workers' Compensation Board database).

Unfortunately, conservative treatments available to these patients are limited, and usually only provide short-term relief of symptoms, if any [8]. Although surgical decompression of the carpal tunnel is considered to be the definitive treatment, it is not without problems. For instance, the time required for recovery after operation results in loss of income and productivity. Also, in cases that have already undergone severe axonal loss, the symptoms and impairment in hand function may persist [9].

The focus of the present thesis is to address the functional impairment of the hand caused by CTS. We introduced valid and reliable dexterity tools to quantify hand functional impairment and explore the effectiveness of therapeutic interventions tailored for different severities of CTS. To set the backdrop for the investigative themes of this thesis, this introductory chapter covers three main areas. First, it provides a background description of CTS. Second, it reviews the structure and functions of peripheral nerves and the pathophysiology of compression nerve injury. This knowledge is critical in understanding the presentation of CTS and the development of therapeutic interventions. Lastly, it summarizes the objectives of the thesis projects.

1.1 Nerve compression within the carpal tunnel:

To provide a clear understanding of CTS, the following sections review the anatomic aspects of the carpal tunnel and the median nerve, as well as the clinical manifestations associated with median nerve entrapment.

1.1.1 Anatomy of the carpal tunnel:

The oval shaped carpal tunnel is a constrained space demarcated by eight carpal bones at the base, and the transverse carpal ligament at the top. It extends from the distal wrist flexor crease to the base of the metacarpal bones. Carpal bones are arranged in two rows, forming a C-shaped arcade: the proximal row comprises of scaphoid, lunate, triquetrum, and pisiform bones and in the distal row, trapezium, trapezoid, capitate and hamate (Fig. 1.1). The transverse carpal ligament, also known as flexor retinaculum, is composed of a dense bundle of interwoven connective tissue [10]. It is attached to the hook of the hamate and the pisiform on the ulnar side of the hand and to the scaphoid tubercle, trapezium and sometimes the styloid process of the radius on the radial side.

The width of the carpal tunnel is 20 mm at its narrowest region at the hook of the hamate, and 26 mm at its widest region at the outlet [11]. The depth of the tunnel also varies from 10 mm by the hook of the hamate to 13 mm at the outlet. Consequently, at the level of the hook of the hamate an hour-glass stricture is formed, which is the prime location for compression of the tunnel contents. Indeed, MRI studies in cadavers show that the ratio of the carpal tunnel contents to the tunnel area is significantly higher at this level compared to the tunnel inlet and outlet [12]. The second potential site of nerve compression is at the level of the proximal edge of the transverse carpal ligament, which is the area of transition from the forearm fascia to the transverse carpal ligament [11]. This is the probable site for flexion-induced deformation of the median nerve.

1.1.2 Carpal tunnel contents and pressure:

The carpal tunnel is a passage that connects the forearm to the hand through which 10 structures course. Of these, nine are tendinous that include 4 flexor digitorum superficialis tendons, 4 flexor digitorum profundus tendons, and the flexor pollicis longus tendon. The most superficial structure, which is also the most susceptible to compression, is the median nerve which lies just beneath the flexor retinaculum (Fig. 1.1). It enters the tunnel at the midline or slightly to the radial side. The contents of the carpal tunnel are tightly arranged in this space. This can easily induce high pressure on the median nerve within the tunnel. The average intracarpal pressure in healthy subjects is 2.5 mm Hg when the wrist is at the neutral position [13]. However, this pressure rapidly increases three to six times just from flexion and gliding of the tendons within the tunnel alone [14]. The mean intracarpal pressure in CTS subjects was found to be 43 mm Hg that increased to a mean of 167 mm Hg upon active grip [15]. This pressure reverts to normal after the decompression surgery. An intracarpal pressure of 30 mm Hg is sufficient to initiate changes in the function of sensory and motor nerve fibers [16]. Therefore, it is conceivable that any increase in the volume of the intracarpal contents (e.g. tendonitis), or reduction in the tunnel space (e.g. fluid retention due to pregnancy and hypothyroidism) can increase intracarpal pressure and thus compress the median nerve. Details of nerve injuries caused by extraneural pressure are discussed later in this chapter.

1.1.3 Median innervation of the hand:

Fibers from the medial and lateral cord of the brachial plexus join to form the median nerve at the level of axilla. The median nerve is derived from C5, C6, C7, C8 and T1 nerve roots even though anatomic variations lacking C5 or T1 root contribution have been reported [17]. It is a mixed sensory and motor nerve that provides the innervation of the hand through its palmar cutaneous branch, recurrent thenar motor branch, the digital nerves, and lumbrical branches. Understanding the innervation territory of the median nerve is important in understanding the hand symptoms associated with CTS.

The palmar cutaneous branch originates 5 to 8 cm proximal to the distal wrist crease, courses above the flexor retinaculum when entering the hand. It provides sensory innervation to the thenar eminence and the proximal palm. This nerve is spared from compression in CTS because the branch does not travel through the carpal tunnel. Other branches of the median nerve originate within or distal to the carpal tunnel, therefore undergoing compression injury in CTS.

The recurrent branch provides motor innervation to the abductor pollicis brevis (APB), opponens pollicis, and flexor pollicis brevis muscles in the thenar eminence. These muscles are involved in raising the thumb perpendicular to the palm, flexing the metacarpal bones, and adducting and flexing the proximal phalanx of the thumb respectively. Other thenar muscles are adductor pollicis and deep head of the flexor pollicis brevis which are innervated by the ulnar nerve. Sensation of the index and the middle fingers, medial aspect of the thumb and the lateral side of the ring finger are supplied by the digital branches of the median nerve (Fig. 1.2). Additionally, they innervate the distal palm adjacent to the base of the thumb, index, middle and lateral half of the ring digit. On the dorsal aspect, tips of the thumb, index, middle, and lateral half of the ring fingers are innervated by digital nerves up to the distal interphalangeal joints. The most common variation is the innervation of the ring digit: it can be innervated solely by the median nerve or the ulnar nerve. Another common variation is innervation of the palmar aspect of the thumb by the superficial radial nerve.

Motor branches to the first and second lumbrical muscles arise from the digital branches. The role of the lumbrical muscles is to extend the interphalangeal joints and flex the metacarpophalangeal joints. The most common variation is partial median innervation of the third lumbrical to the ring finger. Besides the motor and sensory branches, the median nerve provides sudomotor and vasomotor sympathetic innervation to the skin and blood vessels respectively. The sympathetic distribution of the median nerve at the palm matches its sensory innervation territory.

1.1.4 Manifestations of carpal tunnel syndrome:

At the early stages, CTS is clinically characterized by intermittent numbness and tingling primarily in the median sensory innervation territory of the hand: the thumb, index, middle and the radial half of the ring finger. However, many patients cannot delineate the distribution of the symptoms [18]. At this stage, pain may be absent or minimal. Patients commonly complain of nocturnal discomfort and interruption of sleep due to sensory symptoms. Also, strenuous manual labor and prolonged positions of the hand such as driving or holding the telephone receiver can precipitate or aggravate the symptoms. Stopping the activity that has caused the discomfort, rubbing and shaking the hand abate the symptoms. Sometimes patients complain of their hands feeling swollen and stiff due to involvement of the sympathetic fibers, even though no visible swelling can be seen [19]. Cutaneous manifestations of CTS, although uncommon, have been reported. Ulcerative, bullous lesions of the skin of the median-innervated fingertips [20], and digital dryness and nail changes have been noted [21]. As CTS progresses, symptoms persist even after changing the hand activities or position. Pain at the wrist and hand, as well weakness starts to develop. The combination of motor weakness and sensory complaints impairs hand function. Patients commonly report unreliability of their grip, fumbling and dropping small objects. Eventually, chronic and severe forms of CTS lead to marked weakness and thenar atrophy.

The examination of CTS patients includes regional arm and neck examination to rule out other causative medical conditions. Common coexisting neurologic conditions include other mononeuropathies, brachial plexopathy, myelopathy, and peripheral neuropathy. Wrist and hand examinations may reveal coexistence of tenosynovitis, deformity, or injury. Sensory and motor assessments are routinely performed for CTS. Common sensory tests check for sensation of pain, vibration and two-point discrimination. Pin prick test examines pain perception by using the tip of a needle. Vibration sensation is examined by placing the tip of a vibrating 256-Hz tuning fork over the dorsal aspect of the proximal interphalangial joint and asking the patient to report the vibration. Two-point discrimination measures the minimum distance between two pins that can be felt as distinct stimuli. Although sensory complaints are the hallmark of CTS, sensory tests may not detect the abnormalities especially in mild and recent onset CTS [22]. In a study on 74 symptomatic hands, Spindle and Dellon [23] detected sensory abnormalities only in 22% when tested for static two-point discrimination, and in 28% when tested for moving two-point discrimination. Abnormal pin prick and vibration sensations were detected in 42% and 57% of hands respectively.

Motor assessment is usually done by examining the strength of median innervated muscles of the thenar eminence. The APB muscle at the thenar eminence is the most reliable one to test since it is unlikely to receive innervations from the ulnar nerve. The thumb is raised perpendicular to the palm, and the patient resists the pressure applied by the examiner against the distal phalanx. The strength of APB is compared with that of the other hand or the strength of other muscles in the same hand. Besides the muscle strength, one also looks for thenar atrophy which presents as softness and loss of its bulk on palpation.

Since the symptoms of CTS are often intermittent in nature, patients may be asymptomatic when presented to a clinician. Therefore, provocative tests are often used to elicit the symptoms. Two commonly used ones are Tinel's and Phalen's tests. Tinel's sign is elicited by percussing the median nerve at the wrist which evokes tingling sensation in the median innervated territory of the hand in CTS patients. Phalen's test involves asking the patient to sustain flexion of the wrist that usually produces tingling and numbness in the median nerve territory within a minute. However, both tests lack sensitivity and specificity [24;25].

1.1.5 Electrodiagnosis of CTS:

Simpson was perhaps the first to report electrophysiologic abnormality in CTS patients, displayed as prolonged transcarpal terminal motor latency [26]. Focal conduction slowness or block can be detected on median motor and sensory nerve conduction studies. Although comparison of the nerve conduction values between two hands is suggested, its utility is limited in patients with bilateral CTS. Therefore, the test results are compared with standard norms [27]. Currently, nerve conduction studies of the median nerve are accepted as gold standard for diagnosing CTS [28].

Measurement of the transcarpal terminal motor latency of the median nerve is a common starting point, because it is less prone to technical problems. In CTS patients, the latency becomes prolonged. However, this abnormality does not appear in the early, mild stage of the disease. Decline in the amplitude or even absence of action potential in motor studies can be seen, although it is neither common nor sensitive [29]. Dispersion of the action potential may be another finding in CTS [30]. Slowing of the forearm segment of the median nerve also occurs due to loss of the fastest conducting fibers in the nerve [31]. Rarely, motor slowing is present without any sensory findings [32].

Sensory nerve conduction studies at the wrist and palm provide a reliable criterion for detecting CTS. Slowing of the sensory conduction velocity is the most sensitive sign of abnormality [18]. Decrease in the amplitude of the sensory nerve action potential, or its absence, is another indicator of median nerve compression at the wrist.

Needle electromyography (EMG) with intramuscular electrodes is not used as commonly as nerve conduction studies in the diagnosis of CTS. If the median innervated muscles of the thenar eminence show abnormalities on needle EMG examination, but the muscles proximal to the compression are normal, a case for CTS can be made. EMG is helpful in case of axonal degeneration since it demonstrates denervation signs such as fibrillations. Therefore, needle EMG examination can be informative in severe cases of CTS.

Techniques for the motor and sensory nerve conduction studies of the median nerve are detailed in section 3.3.3 of this thesis.

1.2. Pathophysiology of the median nerve compression:

1.2.1 The median nerve:

The median nerve is composed of sensory, motor, and sympathetic fibers. The cell bodies of the motor and sensory neurons are located in the ventral horn of the spinal cord and the dorsal root ganglion respectively. The median nerve is comprised of fascicles which contain a collection of nerve fibers. An abundance of connective tissue ensheaths the peripheral nerve. The endoneurium, perineurium, and epineurium are connective tissues that surround nerve fibers, fascicles, and the peripheral nerve respectively [33]. The energy supply required for normal nerve function such as impulse transmission and axonal transport is provided by intraneural vascular system. A vascular plexus of microvessels in the epineurium supplies the smaller vessels running alongside the perineurium. The perineurial vascular system obliquely pierces the perineurium to anastomose with the endoneurial vessels [34;35]. This arrangement forms a blood-nerve barrier between the internal layers of perineurial sheath and the tight junction of the endoneurial vessels [36]. The impact of nerve compression on the disruption of this vascular system is discussed in section 1.2.4.1 of this chapter.

1.2.2 Nerve fibers:

There are myelinated and non-myelinated nerve fibers within sensory nerves. Both types of nerve fibers contain a central axon, which has a core cytoplasm (axoplasm) surrounded by a basal lamina (axolemma). A myelinated axon is wrapped by a chain of Schwann cells. Each Schwann cell ensheaths a segment of the nerve fiber, and segments are separated by a gap known as the node of Ranvier [33]. This gap is occupied by sodium channel clusters that sustain the propagation of action potentials along the length of the nerve [37]. The myelinated internodal portion acts as an insulated area, aiding to accelerate action potential propagation through saltatory conduction at the nodes of Ranvier. Myelinated axons are capable of propagating the action potential at a rate of 3 to 150 m/s [38]. On the contrary, non-myelinated axons conduct at 2 to 2.5 m/s.

1.2.3 Axoplasmic transport:

In peripheral nerves, there is a long distance between the cell body and the axon terminal. Therefore, anterograde and retrograde axoplasmic flows are in place to provide exchange of materials between the cell body and the axon. There are two components in the anterograde axonal transport system. The slow axonal transport (1-6 mm/d) is involved in the transport of structural components such as actin, tubulin, microtubules and microfilaments. Fast anterograde axonal transport delivers the materials with functional roles such as neurotransmitters to the axon terminal at a rate of up to 410 mm/d. Retrograde transport has a rate of 240 mm/d. It returns neurotrophic factors and neurotransmitter vesicles for recycling to the cell body [38].

1.2.4 Nerve response to compression injury:

The impact of graded compression on peripheral nerves has been studied on many animal models, using different methods of nerve compression such as tourniquets [39], inflatable nerve cuffs [40], and tubes [41]. The severity of nerve damage and the resultant changes depend on the magnitude and duration of the extraneural pressure. There is consensus that during the early stages of nerve compression, endoneurial flow, axonal transport and blood supply are disrupted. As the severity or duration of compression increases, mechanical deformities follow.

1.2.4.1 mild/acute nerve compression:

Rydevick et al. has reported the early response of the peripheral nerve to various magnitudes of compression. They used inflatable cuffs around the rabbit tibial nerve to monitor the effect of 10 mm Hg increments in compression, from 0 to 80 mm Hg [42]. These authors showed that interruption of blood flow in epineurial venules is the earliest consequence of compression which occurs at 20-30 mm Hg. As the compression increases, the arteriolar and endoneurial blood flow are also disrupted until the intraneural circulation is completely blocked at 80 mm Hg, rendering the nerve ischemic. Furthermore, acute compression of peripheral nerves increases endoneurial fluid pressure due to endoneurial edema [43]. Endoneurial edema is the result of increased microvascular permeability following direct injury to the capillary walls or secretion of inflammatory cytokines [44-46]. Increased endoneurial fluid pressure causes a miniature compartment syndrome due to lack of elasticity in the endoneurium, thus aggravating the intraneural pressure effect [47]. Another early effect of extraneural compression is disruption of the fast and slow axonal transport in proportion to the magnitude and duration of compression [48;49]. Consequently, transportation of cytoskeletal elements, neurotransmitters, and neurotrophins between the cell body and the axon terminal become interrupted and axonal dysfunction ensues. The vascular changes in the peripheral nerve upon compression corresponds with the early signs of CTS: patients complain of intermittent sensory abnormalities especially in certain hand positions, which recovers by shaking or changing of the position owing to the resumption of the circulation.

1.2.4.2 severe/chronic nerve compression:

Inflammation, fibrin deposits, proliferation of fibroblasts and endothelial cells will eventually lead to endoneurial fibrosis which can be detected 28 days after two hours of compression applied to the rat sciatic nerve [50]. However, as the magnitude or duration of nerve compression increases, mechanical deformations occur. Rydevik and Nordborg have shown that application of a severe compression even for a short period causes demyelination and axonal degeneration [51]. They noted folding, rupture and coiling back of the myelin sheath, and even intramyelin spaces at the area under 200-400 mm Hg shortly after the compression. The late effect of the same experiment demonstrated the occurrence of demyelination presented as very thin or invisible myelin, as well as axonal degeneration. Demyelination and axonal degeneration are commonly noted in chronic forms of nerve compression. Guinea pigs provide a unique animal model for studying chronic median nerve compression since, like humans, they are also susceptible to developing median nerve compression in the carpal tunnel as they grow old [52;53]. Studies on these animals have shown disruption of the myelin in a tadpole fashion; the myelin sheath is thinned at one end of the internode and thickened at the other end. Multiple short remeyelinated internodes are noted in the repaired lesion. In advanced lesions, axonal degeneration and subsequent regeneration happens. Application of pneumatic tourniquet over the baboon limb has shown a nerve lesion characterized by dislocation of the nodes of Ranvier, with invagination of one paranode into the adjacent one. These changes are followed by demyelination and axonal degeneration [54]. Initially, large myelinated fibers are more susceptible to compressive injury compared to small myelinated and unmyelinated nerves [55]. As the compression persists, other nerve fibers undergo the same degenerative changes as well.

1.2.5 Classification of nerve injury:

Seddon described three different stages of nerve damage. The first type, neurapraxia, is represented by disruption of the myelin sheath while axonal continuity is preserved. It results in conduction block and has good prognosis for functional recovery when the insult is removed. The second type, axonotmesis, is represented by disruption of the myelin sheath as well as the axon continuity at the level of the lesion. However, the neural tube remains intact. Subsequently, Wallerian degeneration occurs distal to the lesion. The time required for recovery of this type of nerve injury is the time required for the axon to regenerate and innervate its target tissue. Yet, recovery is feasible due to continuity of endoneurium. The third type, neurotmesis, is represented by disruption of the endoneurial tube, perineurium and epineurium. This is the most severe form of nerve injury that indicates occurrence of nerve severance or scar tissue formation. Therefore, spontaneous recovery is unlikely [56].

In the case of CTS, as a result of the compression of the median nerve, the nerve fibres undergo neurapraxia or axonotmesis depending on the severity and duration of the compression.

1.2.6 Nerve regeneration in crushed nerves:

Peripheral nerves that have undergone neurapraxia remyelinate their axons. Proliferating Schwann cells are involved in this phenomenon, and the new myelin sheath is significantly thinner than that of normal axons. As remyelination proceeds, a pattern of shorter segments of myelin emerges to encase the demyelinated areas [57].

After disruption of their continuity, axons of peripheral nerves undergo characteristic changes known as Wallerian degeneration. Typical changes include an increase in the cell body volume, displacement of nucleus to the periphery of the cell body, and disappearance of basophilic material from the cytoplasm (chromatolysis). These changes reflect alteration in the concentration of RNA containing material necessary to bring about a growth supporting state in the axon. Synthesis of proteins that are required for axonal growth such as "growth associated proteins" (GAPs) enhances. Also, the axonal transport increases in favor of transferring components that are involved in axonal regeneration rather than synaptic transmission [58]. Again, proliferation of Schwann cells adjacent to regenerating axons facilitates the Wallerian degeneration [59]. They form Schwann cell columns known as bands of Büngner, which guide the re-growing axons to the appropriate innervation pathway. The rate of axonal regeneration varies depending on animal species and type of nerve injury. In rabbits and rats the rate of regeneration after nerve crush is 3-4.4 mm/d. This speed is slower in humans with a rate of 1-2 mm/d [60]. Recovery after axonotmesis can take many months, especially when the distance between the nerve lesion site and the target muscle is long such as in brachial plexus injuries [61].

1.3 Objectives of this thesis:

In this thesis CTS is used as a prototypical instance of nerve compression injury in humans. Four projects were carried out to address functional and therapeutic issues in CTS:

Project 1: Although Moberg Pick-Up Test has been in use for many years, there were no comprehensive age-matched norms available for it. This is of particular importance since many functional tests are shown to be affected by aging. The Moberg Pick-Up Test is a suitable tool to study the impact of median nerve injury on hand function. Therefore, we carried out this project to establish the age-specific norms for this test to be later used for comparison with CTS patients.

Project 2: Although functional impairment of hands is a common consequence of CTS, there were no valid and reliable tools available to quantify the hand disability. This project was designed to study the validity and reliability of the Purdue Pegboard Test and the Moberg Pick-Up Test to detect hand dysfunction in different severities of CTS.

Project 3: Incomplete or delayed nerve regeneration after axonotemesis injuries is common in patients with CTS. Despite the availability of numerous studies on animals in search for regeneration promoting interventions, no studies had ever been conducted in humans. We used CTS as a model to study the effectiveness of 1-hour electrical stimulation on enhancement of nerve regeneration in humans, in a randomized controlled trial.

Project 4: A useful conservative treatment for CTS is injection of corticosteroids into the carpal tunnel. However, its use has never gained popularity because of its invasiveness. To address this barrier, a non-invasive mode of delivering the medication to the carpal tunnel is needed. We carried out a double blind randomized study to examine the effectiveness of corticosteroid delivered through iontophoresis.

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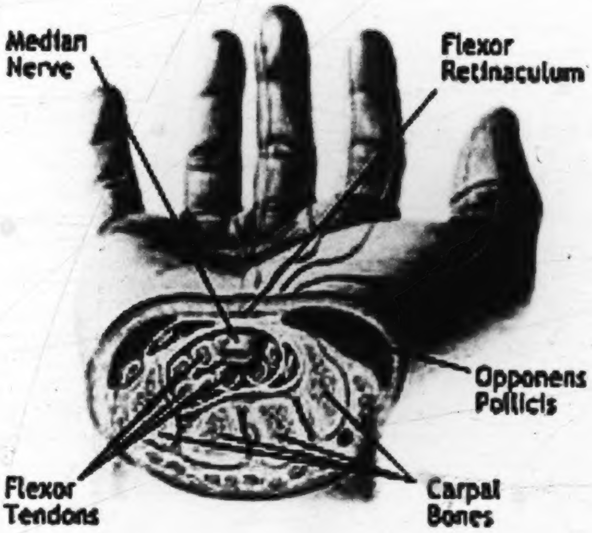
Median Nerve
Flexor Retinaculum
Opponens Pollicis
Flexor Tendons
Carpal Bones

Figure 1.1. Anatomy of the carpal tunnel.

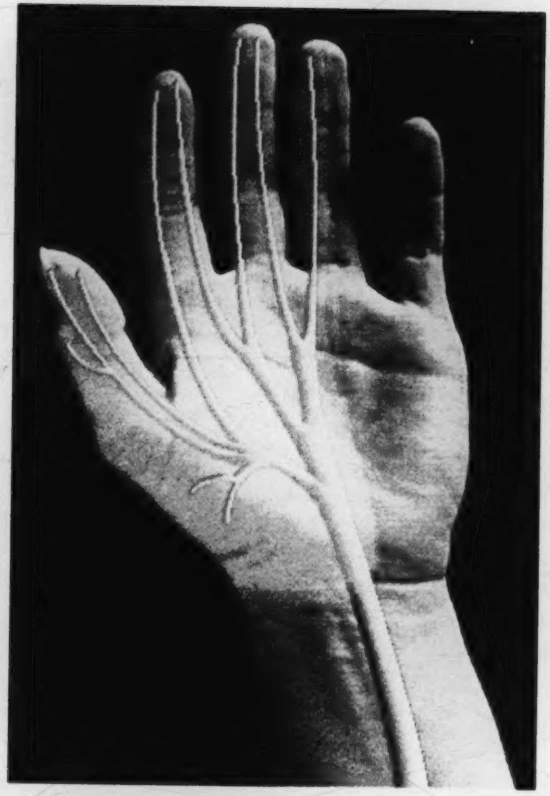

Figure 1.2. Median innervation territory at the palm.

Chapter 2

Normative Values and the Effects of Age, Gender and Handedness on the Moberg Pick-Up Test

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2.1 Introduction:

Somatosensory inputs are important determinants of motor performance executed by the upper limbs [1-3]. In particular, the fingertips rely heavily on tactile afferents for sensory information to distinguish the object shape, mass, mass distribution, and the friction of the grasp that is necessary for fine motor control [2;4]. Therefore, any disruption of sensations at the fingertips can compromise fine motor dexterity of the hand [5]. Unfortunately, pure sensory tests such as pressure threshold, pain, temperature and vibration do not accurately reflect hand function, which is also dependent on motor innervation and muscle function [6]. To fill this void, Moberg introduced a test to quantify hand dexterity [7]. However, the application of the Moberg Pick-Up Test is currently limited because there are no comprehensive normative values for this test. Dellon's normative values for the Moberg Pick-Up Test came from a small sample of only 10 subjects [8]. Ng et al. subsequently conducted a study on 100 healthy subjects [9]. However, the majority of these subjects were in the younger age groups: 53% were 20—29 years old, and 19% were 30—39 years old. Therefore, their normative values were clearly biased towards younger subjects. This is an important consideration since aging has been shown to reduce hand function and sensitivity by tools such as Semmes-Weinstein Monofilaments, two point discrimination, and the Purdue Pegboard Test [10-12]. In contrast, a large portion of patients with peripheral nerve ailments such as carpal tunnel syndrome are middle aged or older. Therefore, using the normative values of healthy young adults to gauge the hand function of older subjects can be misleading.

The present study was carried out to test the hypothesis that performing the Moberg Pick-Up Test is significantly influenced by the age of subjects. Additionally, we investigated the impact of gender and handedness of subjects on their hand function. We hypothesized that female subjects carry out this test faster than male subjects, and the subjects' dominant hand is more skilled in task performance than their non-dominant hand.

2.2 Methods:

2.2.1 Subjects:

This study complied with the guidelines of and was approved by the Human Research Ethics Board at the University of Alberta. The study was advertised at the university, seniors' residences and recreation centers in Edmonton for subject recruitment. One hundred and sixteen healthy subjects, 87 female and 29 male, participated in the study. Subjects between 20 and 89 years old were categorized into three groups: 1) young; 20—39 years old, 2) middle aged; 40—59 years old, and 3) older; 60 years and above. They represented a wide variety of occupations including students, laborers, nurses, clerks and retirees. The exclusion criteria were: 1) subjective sensory or motor complaints in the upper extremities such as numbness, tingling, and weakness, 2) upper extremity deformities, 3) movement disorders such as Parkinson's disease, 4) documented peripheral neuropathies, and 5) presence of predisposing factors to peripheral neuropathies such as hypothyroidism and diabetes. These participants were all interviewed by the examiners, and were deemed to be eligible for the study. They all gave their informed consent.

2.2.2 The Moberg Pick-Up Test:

Twelve objects were spread randomly on a 45 × 29.5 cm wooden platform, next to a container. These objects were: wing nut, screw, key, nail, Canadian nickel, Canadian quarter, washer, safety pin, paper clip, large and medium hexagonal nut, and small square nut. Subjects were seated in front of the wooden platform that was placed on a table lengthwise. The platform was used to keep the dispersion of items within consistent limits for all subjects. Test objects were all placed on the platform at the same side as the hand which was to be tested while the container was placed at the opposite side (Fig. 2.1).

Subjects were instructed to start picking up the items one at a time and place them in a 15.5 cm wide round container as fast as possible. Their performance was timed with a stopwatch. Subjects were requested to neither slide the objects on the platform nor use their D4 and D5 digits. This test was performed in two phases: 1) with eyes open, and 2) with eyes closed. For each phase of the test the dominant hand, defined as the one used for writing, was tested first. Each part of the test was repeated three times to obtain an average. The instructions to perform the two phases of the test were identical except for two additions to the second phase: firstly, subjects were asked to hold the container with the opposite hand since they had their eyes closed. Secondly, when only two or three objects were left on the platform they were informed of the number of remaining items. This helped to avoid the tendency to count the objects while performing the task, and thus getting distracted.

2.2.3 Statistical Analysis:

The statistical program SPSS 12.0 for Windows was used in this study. The Shapiro-Wilk Test of normality was used to assess whether the results have a bell shaped distribution. It revealed that the results were significantly skewed from a gaussian distribution ($P < 0.05$). Therefore, non-parametric tests were used for subsequent data analysis.

The Kruskall-Wallis Test was applied to test the overall impact of age on performing each subset of the Moberg Pick-Up test. Furthermore, we used the Mann-Whitney U Test to compare the hand function of the three age groups.

The Mann-Whitney U Test was also used to examine the impact of gender on hand function. We finally compared the function of the dominant and non-dominant hands by using the Wilcoxon Signed Ranks Test. The level of probability accepted as being statistically significant was $p < 0.05$.

2.3 Results:

Age had a significant impact on hand function: young, middle aged and old subjects required a maximum time of 11.6, 13.1, and 14 seconds (s) ($p<0.01$) respectively to perform the test using the dominant hand, and 12.4, 13.7, and 14.5 s ($p<0.05$) using the non-dominant hand, with eyes open (Fig. 2.2). This maximum time is based on the upper bound of 95% confidence interval. The performance of each age group was significantly different from the other two, with young subjects being the fastest and the elderly group being the slowest to perform the test ($p<0.05$). When subjects closed their eyes, this score increased to 22.7, 24.3, and 25.4 s

($p<0.05$) for the dominant hand, and 22, 24.6, 27 s ($p<0.05$) for the non-dominant hand in young, middle aged, and older subjects respectively (Fig. 2.3). The only exception was the absence of a statistical significance between the young and middle aged subjects when performing the test using their dominant hand with eyes closed ($p=0.22$).

To study the impact of gender on hand function, we combined the data pertaining to the three age groups. Female subjects carried out all subsets of the Moberg Pick-Up Test significantly faster than the male subjects ($p<0.05$): female subjects took a maximum time of 12.5 s to perform the test using their dominant hand, and 13.3 s for the non-dominant hand with eyes open (Fig. 2.4). When vision was occluded, this value increased to 23.4 s for the dominant hand, and 24 s for the non-dominant hand (Fig. 2.5). Male subjects, however, took a maximum time of 14.3 s using their dominant hand, and 14.7 s using their non-dominant hand with their eyes open to finish the task (Fig. 2.4). Closing the eyes prolonged the completion of the test to 26.3 s with the dominant hand, and 27 s with the non-dominant hand (Fig. 2.5).

Subjects performed the test faster with their dominant hand ($p<0.05$) than the non-dominant hand. With eyes open, the maximum time consumed by the dominant hand to complete the test was 13 s compared to 13.4 s consumed by the non-dominant hand. Closing the eyes prolonged this time to 23.9 s for the dominant hand, and 24.4 s for the non-dominant hand (Fig. 2.6). The age and gender specific normative values based on the upper bound of 95% confidence interval are detailed in table 2.1.

2.4 Discussion:

Although deterioration of sensory and motor capabilities of the hand due to aging has been reported by several studies [10;13], its impact on executing the Moberg Pick-Up Test has not been systematically evaluated. The present study confirmed that performance of the Moberg Pick-Up Test differed significantly among the young, middle aged and old subjects. Although the difference between the hand function of the young and middle aged subjects using their dominant hand with eyes closed did not reach a statistical significance, it nevertheless followed the same trend as the other subsets of the test.

Because of the large sample size and that the subjects represented various occupations, the results of this study serve as useful normative values against which patients with different ailments can be compared.

Compared to other tests for hand dexterity, the Moberg Pick-Up Test has a number of major advantages. First, the test only requires relatively simple equipment and it assesses the dominant and non-dominant hands separately. In addition, the test consists of a second phase in which subjects repeat the test with their eyes closed, thus assessing the sensory acuity at the fingertips.

To our knowledge, this is the only study that has systematically evaluated the effects of age, gender and handedness on the Moberg Pick-Up Test. In addition to small sample size, Delon's normative values cannot be directly compared with other studies because he replaced the object manipulation with closed eyes with the object recognition instead [8]. In agreement with our contention about the study by Ng et al., their results are comparable to the hand function of the young subjects in our study [9].

Our observation that females performed the Moberg Pick-Up Test faster than males is in agreement with other investigators [9]. Also in conformity with Ng et al., we demonstrated that the dominant hand is statistically faster in executing this test than using the non-dominant hand.

The Moberg Pick-Up test is a good test for hand function especially when it involves the median innervation territory. Disruption of sensations at the fingertips which leads to hand disability commonly follows insults to the median nerve such as trauma, nerve compression, or peripheral neuropathies. These conditions can affect patients in a wide age range. Therefore, age specific norms for this test are crucial. Although not tested in this study, given the relatively simple nature of this test, the inter rater reliability of this test is likely to be high. Indeed, this was shown by Ng et al. in 14 subjects [9].

Apfel introduced a hand function test that is similar to the first phase of the Moberg Pick-Up Test [14]. In that test, subjects were timed when they put 19 objects, one at a time, into a container. The Apfel Test shares some of the Moberg Pick-Up Test items such as wing nut, paper clip, and safety pin. However, most of the other items such as toilet paper role, table tennis ball, match box and wooden blocks are large enough to be picked up easily without relying heavily on sensitivity at the fingertips. This is an important point of distinction since that test is performed only with the eyes open.

This study did not investigate the impact of subjects' occupation on their hand function. This factor may contribute to the manual dexterity, and to some of the differences noted among different age groups and genders. Therefore, further studies that examine the effect of occupation on the performance of subjects on the Moberg Pick-Up Test are warranted.

Reference List

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Table 2.1
Normative values

	Young (20-39 y.o)		Middle aged (40-59 y.o)		Old (60+ y.o)	
	Female N=25	Male N=9	Female N=24	Male N=11	Female N=38	Male N=9
Eyes open						
Dominant hand	12.0	12.3	12.6	16.5	16	16.8
Non dominant hand	12.5	14	13.3	18	18	15.4
Eyes closed						
Dominant hand	23.8	22.5	23	30.6	27.8	29.9
Non dominant hand	23.6	21.6	24.1	31.6	31.5	31.23

Normative values for the Moberg Pick-Up Test based on the age and gender of subjects. Values represent the upper bound of 95% confidence interval for mean.

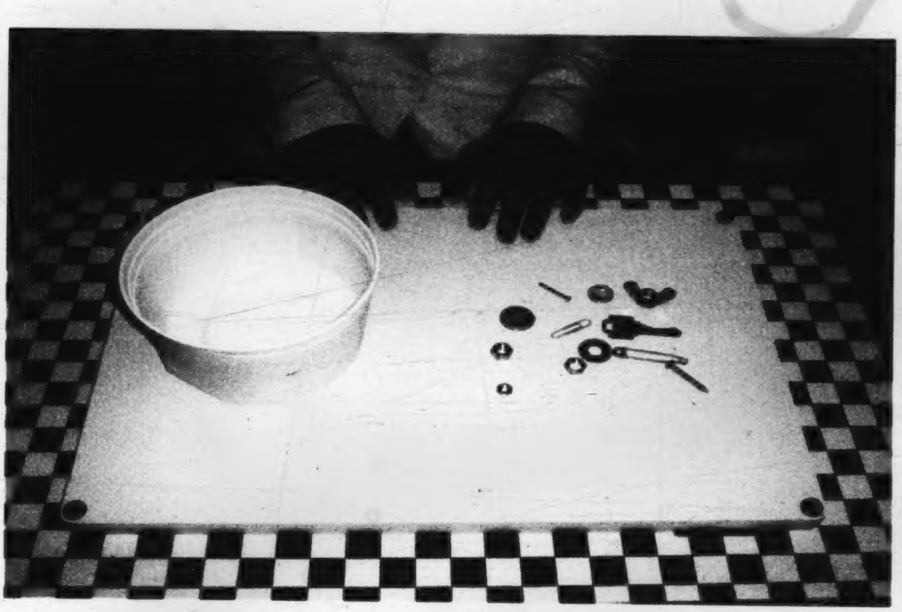

Figure 2.1. Presentation of the Moberg Pick-Up Test.

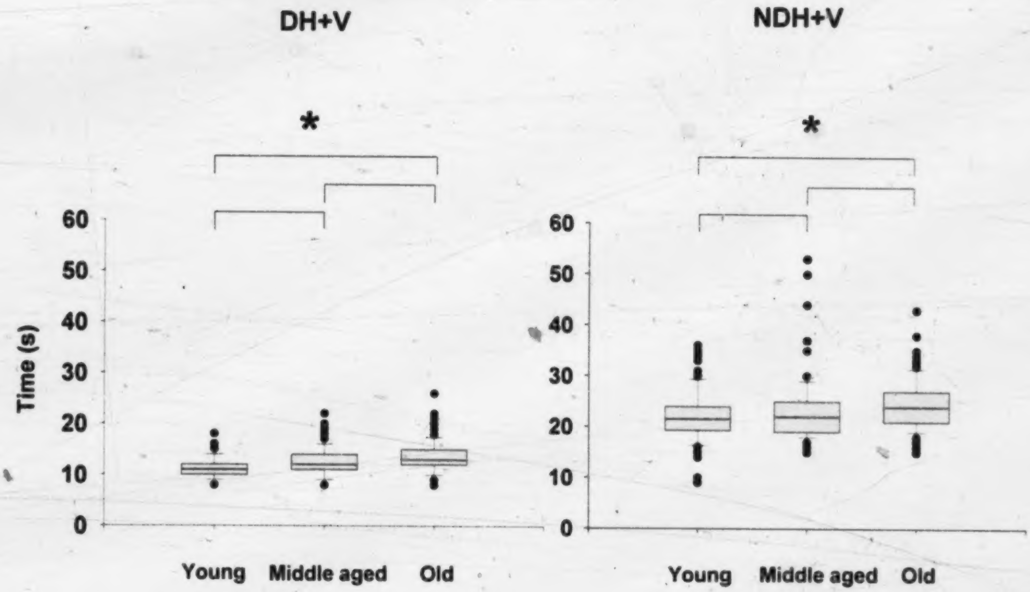

Figure 2.2. Impact of the age of subjects on performing the Moberg Pick-Up Test with eyes open. DH+V=dominant hand with eyes open. NDH+V=non dominant hand with eyes open. Box plots represent the median (middle line), 75th and 25th percentiles (upper and lower limits of the box plot). The upper whisker represents 90th percentile, and the lower whisker represents the 10th percentile. Black dots show the entire range. * denotes statistical significance at $p<0.05$

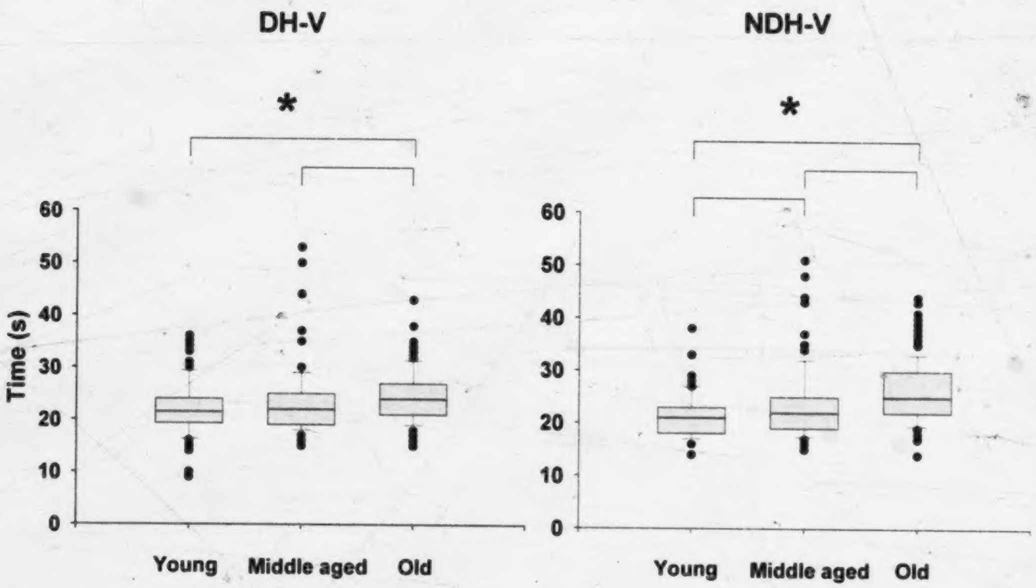

Figure 2.3. Impact of the age of subjects on performing the Moberg Pick-Up Test with eyes closed. DH-V=dominant hand; eyes closed, NDH-V=non-dominant hand; eyes closed. Box plots represent the median (middle line), 75th and 25th percentiles (upper and lower limits of the box plot). The upper and lower whiskers represent 90th and 10th percentiles respectively. The middle line in DH-Vplot for young subjects has overlapped with the 25th percentile. Black dots show the entire range.* denotes $p<0.05$.

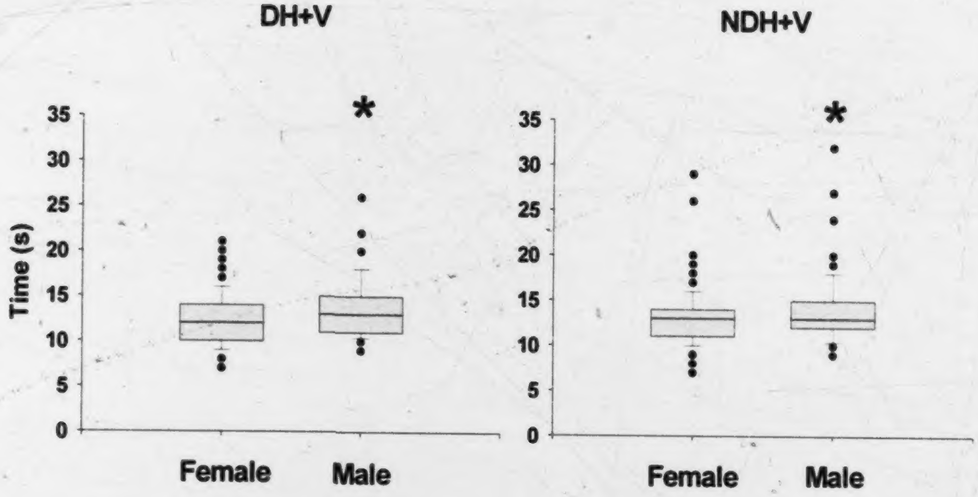

Figure 2.4. Impact of the gender of subjects on performing the Moberg Pick-Up Test with eyes open. DH+V=dominant hand with eyes open. NDH+V=non-dominant hand with eyes open. Box plots represent the median (middle line), 75th and 25th percentiles (upper and lower limits of the box plot). Upper and lower whiskers represent the 90th and 10th percentiles respectively. Black dots show the entire range.
* denotes $p<0.05$

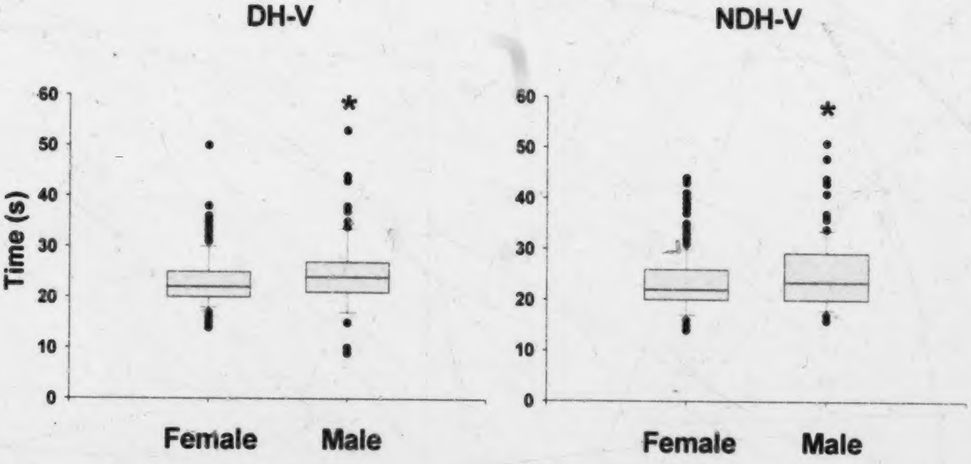

Figure 2.5. Impact of gender of subjects on performing the Moberg Pick-Up Test with eyes closed. DH-V=dominant hand with eyes closed. NDH-V=non-dominant hand with eyes closed.
Box plots represent the median (middle line). 75th and 25th percentiles (upper and lower limits of the box plot). Upper and lower whiskers represent the 90th and 10th percentiles respectively. Black dots show the entire range. * denotes $p<0.05$.

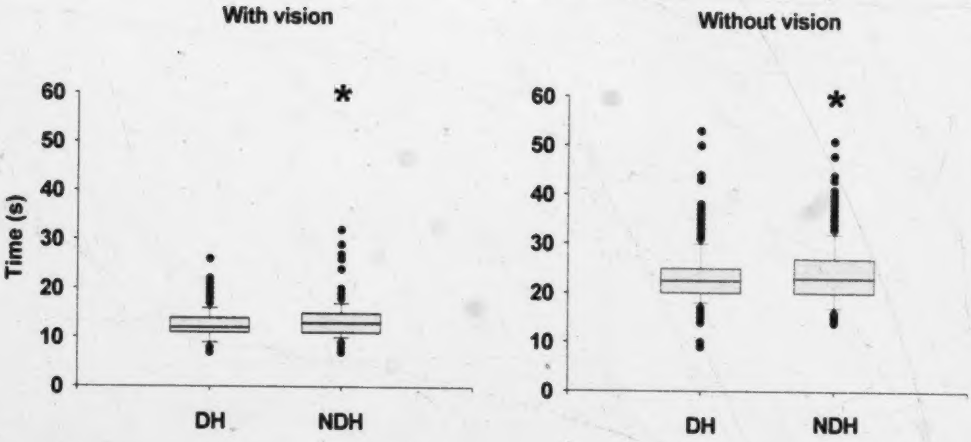

Figure 2.6. Comparison of the skillfulness of the dominant and non dominant hand in executing the Moberg Pick-Up Test.
DH=dominant hand, NDH=non-dominant hand. Box plots represent the median (middle line), 75th and 25th percentiles (upper and lower limits of the box plots). The upper and lower whiskers represent the 90th and 10th percentiles respectively. Black dots show the entire range. * denotes $p < 0.05$.

Chapter 3

Validity and Reliability of the Purdue Pegboard Test and the Moberg Pick-Up Test in Patients with Carpal Tunnel Syndrome

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3.1 Introduction:

Carpal tunnel syndrome (CTS) is the most common peripheral nerve disorder with a prevalence as high as 9 % among the general population [1]. It is caused by compression of the median nerve within the carpal tunnel located at the base of the palm. Since the median nerve is responsible for a large portion of the sensory and motor innervation of the hand and forearm, its compression can severely compromise hand function [2;3]. It not only affects grip and pinch strength but also numbness and tingling at the fingertips. This can have major functional implications whether the individual is engaged in heavy repetitive manual labor or in occupations that involve fine motor tasks [4].

Although much effort has been spent on improving the accuracy of the diagnosis and gauging the effectiveness of treatments for CTS, current literature heavily relies on nerve conduction studies (NCS) and subjective patient self-reporting as yardsticks to determine the severity of hand functional disability and the outcome of treatments [5-7]. Yet, the electrodiagnostic findings often do not correlate well with the severity of symptoms or with the functional limitations of the hand [8-11]. These discrepancies have practical implications when tailoring treatments, rehabilitation strategies, and evaluating the effectiveness of these interventions.

To fill this void, a valid and reliable tool to measure fine motor function in CTS patients is needed. However, a standardized, valid hand function test with proven reliability for CTS is not currently available. For example, the Wisconsin Test Battery developed by Jeng et al. [12-15] examines the sensory and motor components separately. While the repetitive rapid pinch and release test that it employs is involved in some occupational tasks, it does not closely resemble many other activities of daily life in the general population. Therefore, the Wisconsin Test Battery cannot be considered a comprehensive hand function test.

To identify potentially better suited tests, we reviewed the literature for tests that assess fine motor activities of the hand by employing tasks resembling the activities of daily life and requiring the use of the median innervated territory of the hand. Additionally we balanced it with practical considerations such as cost of the tools, the time required to administer the tests, and their availability in clinical settings. Based on these criteria, we identified two tests, the Purdue Pegboard Test and the Moberg Pick-Up Test, as being potentially suitable for this purpose [16;17].

Normative values and reliability of both tests have been studied extensively [18-22]. The Purdue Pegboard Test has been used as an outcome measure tool in settings such as brain damage [23], Parkinson's disease [24] and multiple sclerosis [25]. The validity of the Moberg Pick-Up Test for the functional assessment of inflammatory joint diseases such as rheumatoid arthritis has been established [26]. Additionally it has been employed as an outcome measure tool to monitor hand function after median nerve laceration [27;28]. However, the validity and reliability of these tests as applied to patients with carpal tunnel syndrome have never been examined.

Therefore, the purpose of this study was to test the following hypotheses: 1) the Purdue Pegboard and the Moberg Pick-Up Tests are valid tools that can quantify the impact of CTS on manual dexterity, and 2) these tests have high inter rater test-retest reliability in detecting the hand function deficits in CTS patients.

3.2 Methods:

This was a prospective cross-sectional study that complied with the guidelines of and approved by the Human Research Ethics Board at the University of Alberta. All subjects gave their informed consent.

3.2.1 Healthy subjects:

Healthy subjects were recruited through advertisements at the University of Alberta, seniors' residences, and recreation facilities in Edmonton. The exclusion criteria were: 1) sensory or motor complaints in the upper extremities such as numbness, tingling, and weakness, 2) upper extremity deformities, 3) movement disorders such as Parkinson's disease, 4) documented peripheral neuropathies, and 5) presence of predisposing factors to peripheral neuropathies such as hypothyroidism and diabetes. All participants were interviewed by the examiners and were deemed to be eligible for the study.

3.2.2 CTS subjects:

Patients were recruited from a university electromyography clinic from a large pool of patients. The eligibility criteria for CTS patients were the presence of any of the symptoms and signs suggestive of CTS: 1) numbness and tingling sensation in the median-innervation territory of the hand, with or without pain, 2) these symptoms were induced by repetitive hand movements or malposition, and were relieved by resting, rubbing and shaking the hand, 3) nocturnal wakening and sleep disturbance by these symptoms, or 4) weakness in thumb abduction and thenar atrophy.

Subsequently, the presence of median nerve compression was confirmed by electrophysiological studies. Patients with arthritic diseases or other neurological conditions, trauma to wrist or arm and previous carpal tunnel release were excluded from the study. We suspected that the functional impairment depends on the severity of CTS. Therefore, we used two separate methods which are commonly used in the literature to classify the severity of CTS as mild, moderate or severe: 1) based on the nerve conduction studies, and 2) based on the Levine's Self-Assessment Questionnaire for CTS scores [29;30].

3.2.3 Nerve Conduction Study:

All sensory and motor nerve conduction studies were performed on patients using a Viking Select EMG machine (Nicolet Biomedical, Minneapolis) by the same examiner (KMC). Sensory and motor nerve conduction studies of the median nerve were done using standard techniques [31].

3.2.3.1 median sensory nerve conduction study:

The hand was cleansed with rubbing alcohol and the skin temperature was maintained between 32 and 34 °C with an infrared lamp. Disposable silver/silver chloride surface strip electrodes (Nicolet VIASYS healthcare), measuring 1x2.5 cm, were used. The reference electrode was placed on the distal interphalangeal joint and the recording electrode on the proximal interphalangeal joint of the third digit. The median nerve was stimulated in mid palm and also just proximal to the distal wrist crease. The conduction velocity of the sensory nerve action potential across the carpal tunnel and its negative peak amplitude were measured.

3.2.3.2 median motor nerve conduction study:

The disposable recording surface strip electrode was placed over the motor point on the thenar eminence muscles and the reference electrode over the dorsal aspect of the first metacarpophalangeal joint. The median nerve was stimulated at supramaximal intensity at the wrist 8 cm proximal to the recording electrode and also at the elbow. The maximal compound muscle action potential amplitude, terminal motor latency and conduction velocity in the forearm were measured.

The ulnar nerve was also examined in all subjects and they were all normal. Additional electromyography was done to rule out other disorders such as brachial plexopathy and cervical radiculopathy as necessary based on the symptoms and physical examination findings [32].

To diagnose and classify the severity of CTS, the electrodiagnostic criteria introduced by Padua et al. were used in this study [29]. In brief, patients with abnormal conduction velocity of the median sensory nerve fibers across the carpal tunnel but normal median terminal motor latency were classified as having mild CTS. If the conduction speed of the median sensory and motor nerve fibers were abnormal but the action potentials were still present, the subjects were categorized as having moderate CTS. Lastly, if the median sensory nerve action potential was absent, the patients were classified as severe.

3.2.4 Levine's Self-Assessment Questionnaire for CTS:

Those patients with confirmed CTS were asked to complete the Levine's Self-Assessment Questionnaire for CTS to correlate the severity of hand disability with symptom severity. Levine's Self-Assessment Questionnaire for CTS is a subjective tool that has been used widely as an outcome measure in clinical trials on CTS [30]. This questionnaire consists of two parts: 1) symptom severity scale comprised of 11 items scored on a Likert scale inquiring about pain, paraesthesia, numbness, weakness, nocturnal symptoms and overall functional status, and 2) functional status scale comprised of eight questions regarding activities of daily life commonly affected by CTS. The symptom severity scores ranged from 1 to 5 with 1 representing no symptoms and 5, very severe symptoms. The functional status scores also ranged from 1: no difficulty to do a task, to 5: inability to do a task (Appendix 1). Levine's Self-Assessment Questionnaire for CTS is considered to be a more sensitive subjective questionnaire for CTS than others such as the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire and the 36-item Short-Form Health Survey (SF-36) [33].

3.2.5 The Purdue Pegboard Test:

The Purdue Pegboard (Model 32020, Lafayette Instrument Company, IN, USA) consists of 50 holes arranged in two parallel columns and pegs, washers, and collars located in four cups at the top of the board. The pegs were placed in cups on the far right and far left of the board that could be conveniently reached by both hands. The pegboard was located on a table crosswise, and subjects sat comfortably in front of it. Subjects were instructed to start the test on a verbal cue, while an examiner timed the test with a stopwatch. The test consisted of four subsets. In the first three subsets, subjects had 30 seconds to fill the holes with pegs initially with the dominant hand (defined as the hand used for writing), then with the non-dominant hand and finally with both hands simultaneously. In the last subset, subjects had one minute to assemble in sequence a peg, a washer, a collar, and finally another washer with alternating hands starting with the dominant one first. Each subset was repeated three times to obtain an average. The test scores equaled the number of filled holes or the pieces assembled, depending on the test subset.

3.2.6 The Moberg Pick-Up Test:

Twelve objects were located randomly on a 45×29.5 cm wooden platform, next to a container. The 12 objects were: wing nut, screw, key, nail, Canadian nickel, Canadian quarter, washer, safety pin, paper clip, large and medium hexagonal nut, and a small square nut. Subjects were seated in front of the wooden platform that was placed on a table lengthwise. The platform was used to ensure consistency of the limits of objects dispersion among all subjects. Test objects were placed at the same side as the hand that was to be tested, and a container was placed at the other end of the platform.

The subjects were instructed to start picking up the items one at a time and place them in a 15.5 cm diameter round container on a verbal cue as fast as possible. Their performance was timed with a stopwatch. Subjects were requested to neither slide the objects on the platform, nor use their D4 and D5 digits. This test was performed in two phases: 1) with eyes open, and 2) with eyes closed. For each phase of the test the dominant hand was tested first. Each part of the test was repeated three times and the average time was used. The instructions to perform the two phases of the test were identical, except with two additions to the second phase. Firstly, subjects were asked to hold the container with the opposite hand since they had their eyes closed. Secondly, when only two or three objects were left on the platform they were informed of the number of remaining items. This helped to avoid the tendency to count the objects while performing the task, and thus getting distracted.

3.2.7 Statistical Analysis:

The statistical program SPSS 12.0 for Windows was used in this study. Using the Shapiro-Wilk Test of normality, we found that the results were significantly skewed from a gaussian distribution ($p<0.05$). Therefore, non-parametric tests were used for all further data analyses.

The Kruskall-Wallis Test was applied to individual subsets of the Purdue Pegboard Test and the Moberg Pick-Up Test to assess the overall impact of CTS on dexterity. We then used the Mann-Whitney U Test to assess the impacts of different severity of CTS on dexterity as compared to the control group. The test-retest reliability for each test was appraised using the interclass correlation analysis of reliability. Additionally, we used the Spearman correlation test to examine whether there was a significant difference between hand functional dexterity as measured by the Purdue Pegboard Test and the Moberg Pick-Up Test.

Finally, binary logistic regression was employed to determine whether there was a significant difference between the severity of CTS based on the NCS criteria and that based on Levine's Self-Assessment Questionnaire for CTS scores. To ensure uniformity of CTS severity in the same subject, only the data belonging to 51 subjects with identical NCS severity in both hands were used.

3.3 Results:

3.3.1 Subjects:

There were 123 control subjects in this study: 92 female and 31 male, aged 20 to 89 years old. Since performance at the Purdue Pegboard Test and the Moberg Pick-Up Test has been shown to be affected by age, we categorized the subjects to three different age groups: 1) young; 20—39 years old, 2) middle aged; 40—59 years old, and 3) elderly; 60 years and more. They represented a wide variety of occupations including students, laborers, nurses, clerks, and retirees. All subjects carried out the Purdue Pegboard Test and 116 of them also carried out the Moberg Pick-Up Test (Fig. 3.1). Additionally, since the electrodiagnostic norms change with senility [34;35], we carried out NCS on 14 healthy elderly subjects to establish the median nerve normative values for our laboratory. These subjects also filled out the Levine's Self-Assessment Questionnaire for CTS before undergoing the test to confirm that their hands were indeed free from any symptoms suggestive of CTS.

The CTS group consisted of 115 eligible subjects, 89 female and 26 male, aged 20 to 86. We confirmed unilateral median nerve compression based on NCS parameters in 31 subjects, and the rest had bilateral median nerve compression. All subjects carried out the Purdue Pegboard Test and 94 of them also carried out the Moberg Pick-Up Test (Fig. 3.1). To examine the test-retest reliability of these tests in CTS, 32 subjects repeated the tests for a second time at inter trial intervals varying from one day to two months. These subjects were from all the age and CTS severity groups.

Because the ratios of male to female subjects in the control and the CTS groups were similar, the data from both genders were analyzed together.

3.3.2 The Purdue Pegboard Test:

The NCS values of each hand was determined separately, which in many instances led to different severities of CTS for the dominant and non-dominant hand in a subject. Therefore, the bimanual function and assembly data were excluded from this part of data analysis. In contrast, Levine's Self-Assessment Questionnaire for CTS provided a single CTS severity score for both hands, making it feasible to classify the four subsets of the Purdue Pegboard Test with a unified severity.

Healthy young subjects inserted a mean of 16 pegs with their dominant hand, 15 pegs with the non-dominant hand, 27 pegs with both hands, and assembled 42 pieces. Middle aged subjects in the control group inserted a mean of 15 pegs with the dominant hand, 14 pegs with the non-dominant hand, 23 pegs with both hands, and assembled 33 pieces. Healthy elderly subjects had a mean score of 13 pegs with the dominant hand, 12 pegs with the non-dominant hand, 20 with both hands, and 26 pieces in assembly (Fig. 3.3).

3.3.2.1 severity of CTS based on NCS: In young subjects, the function of both hands in mild, moderate and severe CTS cases was significantly impaired ($p<0.01$) compared to age matched controls, except for the dominant hand of mildly affected subjects ($p=0.84$). Mild, moderate, and severe CTS cases manipulated a mean of 16, 14, and 13 pegs respectively with the dominant hand, and 14, 14, and 12 pegs with the non-dominant hand (Fig. 3.2).

In the middle age group, all severities of CTS compromised hand function except for the task performance of the moderate cases with their non dominant hand ($p=0.21$). They manipulated a mean of 11 to 13 pegs with either hand (Fig. 3.2).

Elderly subjects with mild CTS showed a comparable performance with their dominant hand to that of the control group, with a mean score of 12 pegs ($p=0.2$), and a faster performance with their non-dominant hand (14 pegs) ($p<0.05$). Moderate CTS affected the function of the dominant hand, reducing its score to a mean of 11 pegs, contrary to the non-dominant hand which had a mean score of 13 pegs ($p=0.15$). Severe CTS significantly reduced the mean score of the dominant hand to 9 pegs and the score of the non-dominant hand to 6 pegs (Fig. 3.2).

3.3.2.2 severity of CTS based on Levine's Self-Assessment Questionnaire for CTS score:

Mild, moderate and severe CTS in young subjects significantly affected performance of the bimanual, assembly, and the non-dominant hand subsets ($p<0.01$) while function of the dominant hand was not different from that of the controls ($p\geq0.07$). They manipulated a mean number of 13 to 14 pegs with the non-dominant hand, 18 to 24 pegs with both hands, and assembled 35 to 37 pieces (Fig. 3.3).

In middle age subjects, CTS of all severities negatively impacted all subsets of the test ($p<0.05$) except for the non-dominant hand function of severely affected cases ($p=0.21$), and assembly in mild cases ($p=0.44$). The mean number of pegs manipulated by the dominant hand and non-dominant hand was 13 pegs with any severity of CTS. This score was 19 to 22 pegs for both hands, and 29 to 30 for the reduced assembly scores (Fig. 3.3).

Moderate and severe CTS in the elderly group significantly compromised hand dexterity compared to the controls in all subsets of the test except for task performance with the non-dominant hand of moderately affected subjects ($p=0.88$). These subjects had a mean score of 9 and 11 pegs for the dominant and non-dominant hands correspondingly. The bimanual subset of the test had a mean score of 16 and 13 in the moderate and severe group respectively, and the corresponding score for the assembly was 23 and 19 pieces. Contrary to expectation, mild CTS group performed the task faster ($p<0.05$) than the control group in all subsets of the test. They manipulated a mean of 14 pegs with the dominant and non-dominant hand, 22 pegs with both hands, and 26 pieces when assembling them (Fig. 3.3).

3.3.3 The Moberg Pick-Up Test:

3.3.3.1 severity of CTS based on NCS: Young healthy subjects performed the test with a mean of 11.2 s using their dominant hand and 12 s using their non-dominant hand, with eyes open. When they closed their eyes, this time increased to 21.6 for the dominant hand and 21.1 s for the non-dominant hand. Young subjects with mild CTS completed the test within 14.3 s with their dominant hand and 14.3 s with the non-dominant hand, with eyes open. With eyes closed, this time increased to 26.1 s for the dominant and 25.4 s for the non-dominant hand. Young subjects with moderate CTS required a mean time of 15.6 s and 14.2 s to execute the test with the dominant and non-dominant hand respectively, with open eyes. With eyes closed, the mean time for test performance increased to 26.4 s for the dominant, and 21.6 s for the non-dominant hand. Consequently, young subjects with mild and moderate CTS had significantly impaired hand function compared to controls ($p<0.05$), with the exception of the non-dominant hand of moderate CTS cases with their eyes closed ($p=0.88$). Young subjects with severe CTS based on the NCS were among those who did not carry out the Moberg Pick-Up Test. Therefore, we cannot comment on the hand function of that particular group (Fig. 3.4).

Middle aged healthy subjects performed the test within a mean of 12.6 s using the dominant hand, and 13.1 s using the non-dominant hand, with eyes open. When they closed their eyes, this time increased to 22.9 s and 23.3 s for the dominant and non-dominant hand respectively. Hand function of middle aged subjects with all severities of CTS was significantly disrupted ($p<0.05$): mild, moderate and severe CTS cases required a mean time of 15.9, 14.9, and 23.2 s respectively to perform the test using the dominant hand, and 17.1, 14.3 and 19.3 s using the non-dominant hand with eyes open. Closing the eyes further accentuated the slowness in task performance by CTS subjects: mild, moderate and severe CTS subjects completed the test in a mean time of 30.5, 26.6, and 34.8 s respectively with their dominant hand, and 32, 26.3, and 34.8 s with their non-dominant hand (Fig. 3.4).

Healthy elderly subjects had a mean score of 13.5 s for the task performance using the dominant hand and 14 s using the non-dominant hand, with eyes open. With eyes closed, the score increased to 24.6 s for the dominant hand and 26 s for the non-dominant hand. Elderly subjects with severe CTS demonstrated a markedly impaired hand function in all the subsets of the test. They took a mean time of 26.4 s and 31 s to execute the test with their dominant and non-dominant hand respectively, with eyes open. When they closed their eyes, these scores almost doubled and reached a value of 33.2 s for the dominant hand and 91.1 s for the non-dominant hand. However, the hand function of moderately affected individuals was significantly poor only in two subsets: non-dominant hand with eyes open (17.5 s), and dominant hand with eyes closed (23.2 s). Other test subsets were comparable to the healthy group ($p>0.1$). Also, mild CTS did not affect dexterity in the elderly ($p\geq0.4$) except for the function of dominant hand with eyes closed which took a mean of 24.8 s to be completed ($p<0.05$) (Fig. 3.4).

3.3.3.2 severity of CTS based on Levine's Self-Assessment Questionnaire for CTS score: Contrary to our observation on NCS, some of the young subjects rated their symptoms to be severe on the Levine's Self-Assessment Questionnaire for CTS. The dominant hand function of mild cases in this age group was impaired, both with and without vision, with a mean score of 12.6 s and 24.4 s respectively ($p<0.05$), whereas the non-dominant hand function was not different from controls ($p\geq0.06$). Young subjects with moderate CTS had significantly impaired performance in all subsets of the test ($p<0.005$) (Fig. 3.5). They spent 17.8 s with the dominant hand, and 15.4 s with the non-dominant hand to do the test with eyes open, 31 s with the dominant hand, and 26.7 s with the non-dominant hand with closed eyes. The hand function of young subjects with severe CTS was compromised when performing the test with eyes open: the mean score was 14.9 s for the dominant hand and 14.4 s for the non-dominant hand. However, this effect disappeared when vision was occluded ($p \geq 0.21$), with a score of 23.6 s for the dominant hand and 22.1 s for the non-dominant hand.

In middle age group, those with moderate and severe CTS were significantly slower in all subsets of the test ($p < 0.001$) (Fig. 3.5). The moderately affected subjects took a mean time of 16.6 s to perform the test using the dominant hand and 15.1 s using the non-dominant hand with eyes open, and at least 28.4 s for the dominant hand and 27.6 s for the non-dominant after occlusion of the vision. Severely affected subjects required a mean time of 20.2 s and 20.1 s to execute the test with their dominant and non-dominant hand respectively, with eyes open. After occlusion of the vision, this time increased to 34.7 s and 35.9 s correspondingly. Subjects with mild CTS showed a poor performance with both hands only when their vision was occluded, with a mean score of 25.5 s for the dominant and 25.3 s for the non-dominant hand ($p < 0.05$).

Elderly subjects with severe CTS demonstrated impaired dexterity in all subsets of the test ($p < 0.001$) (Fig. 3.5). The mean time required for the dominant and non-dominant hand to finish the task was 23.8 s and 25.5 s respectively, with eyes open. When vision was occluded this time was further prolonged to 40 s and 70.7 s. Moderate CTS had a similar negative effect except for the function of the non-dominant hand with eyes closed with a median score of 29.5 s ($p = 0.26$). This score was 18 s and 15.7 s for the dominant and non-dominant hands with eyes open respectively, and 34.1 s for the dominant hand with eyes closed. Mild CTS did not have an impact on manual dexterity of the elderly ($p \geq 0.059$).

3.3.4 Test-retest reliability:

The interclass correlation was highly significant for both the Purdue Pegboard Test and the Moberg Pick-Up Test when repeated by CTS subjects ($P<0.001$). The Cronbach's alpha was 0.98 and 0.91 for the Purdue Pegboard Test and the Moberg Pick-Up Test respectively (Fig. 3.6).

3.3.5 Correlations:

We detected a significant negative correlation between the hand function assessed by the Purdue Pegboard Test and the Moberg Pick-Up Test ($p<0.001$) when performing the tasks with the dominant ($r = -0.6$) and non dominant hand ($r = -0.54$)(Fig. 3.7).

Comparing classification of disease severity based on NCS results to Levine's Self-Assessment Questionnaire for CTS score, there was a marked lack of concordance (Table 3.1). The concordance of CTS severity based on the two methods was only 33% in mild, 51% in moderate, and 0% in severe cases of CTS.

3.4 Discussion:

Although carpal tunnel syndrome is one of the most common work related compensation claims, valid and reliable instruments to quantify hand function are lacking. Performance of the Purdue Pegboard Test and the Moberg Pick-Up Test depend on the median innervation territory of the hand. Additionally, they are simple, noninvasive, time efficient and quantifiable. This is the first study that examines the validity and reliability of these two tests to quantify the dexterity impairment in various severities of CTS.

The findings in this study support our first hypothesis that both of these hand function tests are valid in discriminating the compromise in hand dexterity caused by CTS. It showed that even mild CTS can significantly compromise hand function in the young and middle aged subjects who constitute a major part of the work force. Nevertheless, we observed some discrepancies. For example, middle aged subjects with moderate CTS based on NCS values performed the Moberg Pick-Up Test faster than the mild cases, and young subjects with severe CTS based on the Levine's Self-Assessment Questionnaire for CTS score performed the same test faster than the moderately affected subjects. The most likely reason for this finding is that both the electrophysiologic parameters and self-reported severity scores which are currently used to classify the severity of CTS [5;10;29;36;37] are not ideal surrogate methods to measure the functional impact of carpal tunnel syndrome on daily manual activities. This is evident from the lack of correlation between the severity of CTS based on these two methods in subjects with bilateral CTS (Table 3.1). Sensory nerve conduction studies do not represent the manual dexterity since they reflect the properties of the fastest conducting fibers which are mainly involved in vibration sensation. Also, abnormalities of the motor nerve conduction studies demonstrated as prolongation of terminal motor latency for a few milliseconds may not pose functional consequences. Therefore, electrophysiologic parameters including conduction velocity and distal motor latency have little functional correlates.

A consistent discrepancy in this study was that elderly patients grouped as mild CTS outperformed the age matched healthy subjects. This might be due to the fact that most of the control subjects did not undergo nerve conduction studies, nor did they complete the Levine's Self-Assessment Questionnaire. It is a common experience that asymptomatic old subjects often show mild abnormalities on nerve conduction studies. Therefore, it is conceivable that some of these subjects could have mild but asymptomatic median nerve compression.

The task performance of subjects on both the Purdue Pegboard Test and the Moberg Pick-Up Test were highly correlated: subjects who consumed less time to carry out the Moberg Pick-Up Test manipulated more pieces of the Purdue Pegboard Test. Therefore, we conclude that either test can be used as a valid hand function test for CTS in clinical settings.

Longitudinal follow-up of CTS patients is frequently done for the purpose of monitoring disease progression or effectiveness of therapeutic interventions. Therefore, the availability of hand function tests with proven test-retest reliability for multiple assessments is crucial. To that end, this study established the test-retest reliability of these tests in determining the hand functional disability of CTS patients. The significant degree of agreement between these tests further substantiates the convergence validity and that both are reasonable tests to examine hand dexterity in CTS patients.

The lack of consistent correlation between hand function impairment and severity of CTS based on the NCS and subjective symptom criteria poses a practical dilemma as both criteria are widely used in clinical practice. These inconsistencies highlight the need that to meaningfully evaluate the severity of functional impacts of CTS, standardized hand function tests need to be employed. Functional evaluations are particularly critical in CTS patients since it is a common work related upper extremity disorder. Many of the afflicted workers are engaged in repetitive or strenuous manual labors. Findings from the current study suggest that the Purdue Pegboard Test and the Moberg Pick-Up Test can serve as practical, valid, and reliable tests of hand dexterity in the routine assessment of these patients.

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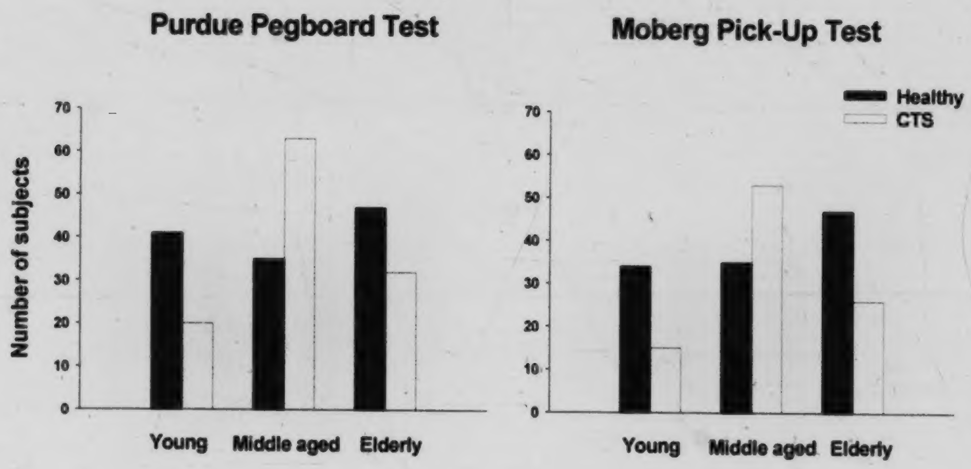

Figure 3.1. Distribution of CTS and control subjects in the three age groups.

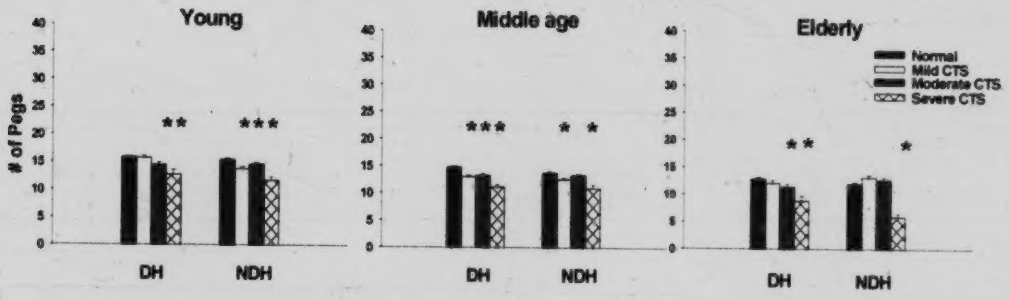

Figure 3.2. Performance of CTS subjects on the Purdue Pegboard Test: severity based on nerve conduction studies.
DH=dominant hand, NDH=non-dominant hand. * denotes $p<0.05$ when the CTS groups were compared with the control group. Error bars represent mean±SE.

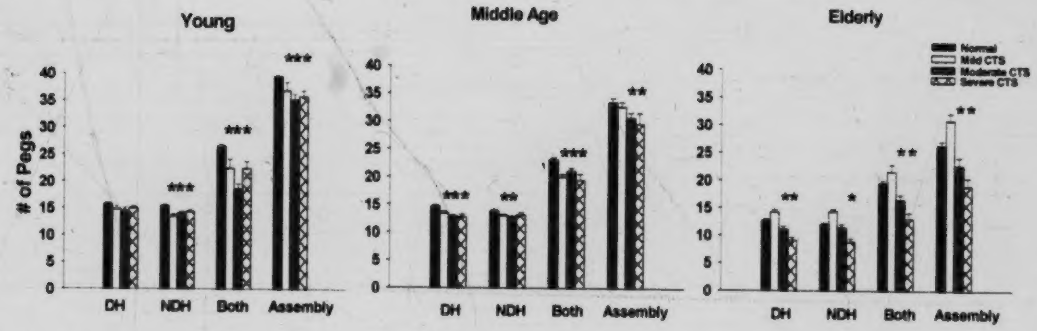

Figure 3.3. Perfromance of CTS subjects on the Purdue Pegboard Test: severity based on Levine's Self-Assessment Questionnaire
DH=dominant hand, NDH=non-dominant hand. * denotes $p<0.05$ when the CTS groups were compared withthe control group. Bars represent mean±SE.

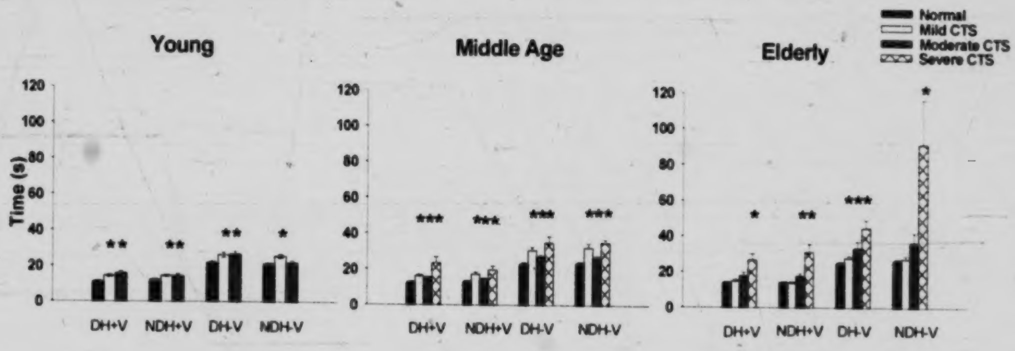

Figure 3.4. Performance of CTS subjects on the Moberg Pick-Up Test: CTS severity is based on nerve conduction studies.

DH+V=dominant hand with eyes open, NDH+V=non-dominant hand with eyes open,
DH-V=dominant hand with eyes closed, NDH-V=non-dominant hand with eyes closed.
* denotes $p<0.05$ when the CTS groups were compared with the control group. Bars represent mean±SE.

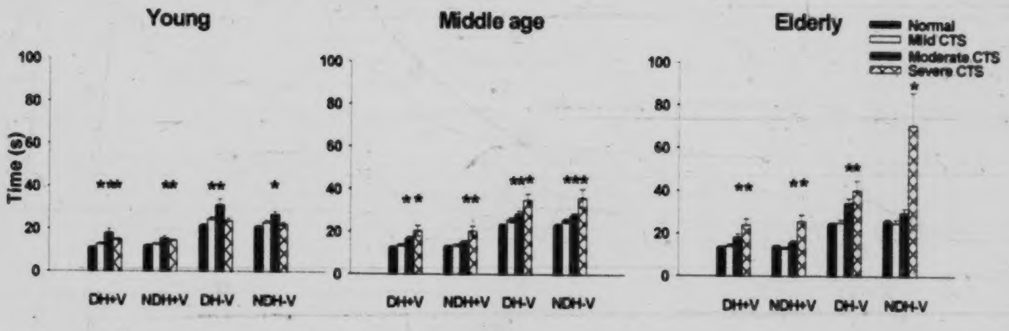

Figure 3.5. Performance of CTS subjects on the Moberg Pick-Up Test: CTS severity is based on Levine's Self-Assessment Questionnaire.
DH+V=dominant hand with eyes open, NDH+V=non-dominant hand with eyes open,
DH-V=dominant hand with eyes closed, NDH-V=non-dominant hand with eyes closed.
* denotes $p<0.05$ when the CTS groups were compared with the control group. Bars represent mean±SE

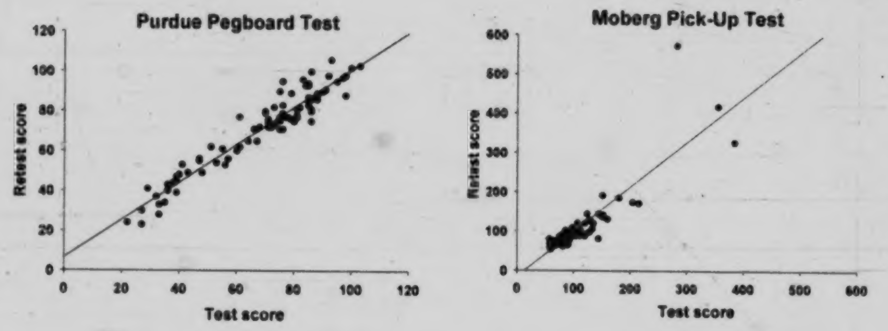

Figure 3.6. Test-retest correlation of the Purdue Pegboard Test and the Moberg Pick-Up Test. The Purdue Pegboard Test score equals the total number of objects manipulated in the four subsets of the test. The Moberg Pick-Up Test score equals the total time consumed to perform the four subsets of the test.

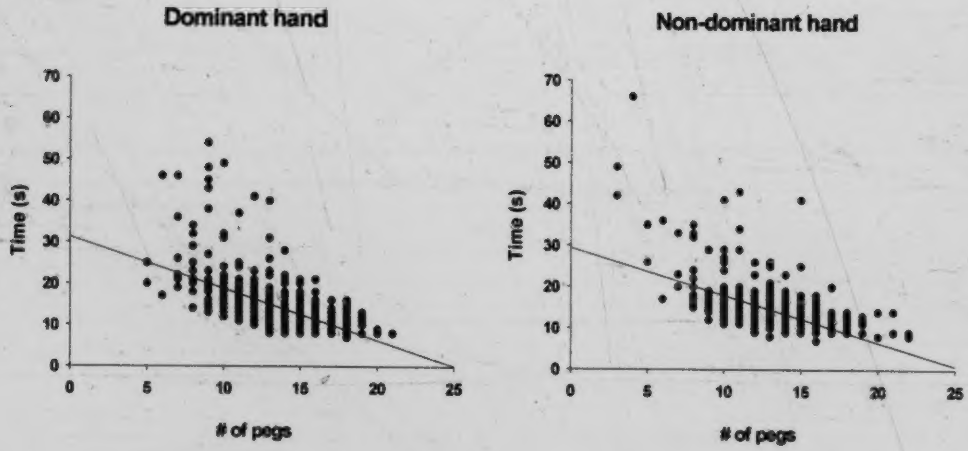

Figure 3.7. Correlation between the Purdue Pegboard Test and the Moberg Pick-Up Test. X axis: hand function on the Purdue Pegboard Test, Y axis: hand function on the Moberg Pick-Up Test.

		Levine's Questionnaire		
		Mild	Moderate	Severe
NCS	Mild	**5**	**5**	**5**
	Moderate	**9**	**17**	**7**
	Severe	**0**	**5**	**0**

Table 3.1. Comparison of CTS severity based on NCS criteria and Levine's Self-Assessment Questionnaire for CTS scores.

Chapter 4

Electrical Stimulation after Decompression Surgery Promotes Nerve Regeneration in Carpal Tunnel Syndrome

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4.1 Introduction:

Even though peripheral nerves have the capability to heal and regenerate after injury, the outcome of recovery depends on the severity of nerve damage. Indeed, failure of functional recovery after nerve injury is common. Therefore, much effort has been directed towards discovering treatment strategies that could enhance nerve regeneration after axonal injury. These include local application of neurotrophic factors [1;2] and thyroid hormone [3] to the transected end of the nerve.

Compared to the above options, electrical stimulation is an appealing intervention to augment axonal regeneration because it is relatively non-invasive. Preliminary evidence of this effect came from pioneering *in vitro* studies. In an early study by Sisken and Smith [4], application of minute direct currents (11.5 nA/mm^2, 12 hours per day for 4 days) on cultured trigeminal ganglia of chick embryos enriched outgrowth of nerve fibers from the explant. These nerve fibers were not only greater in number, but were also longer and more branched than those in control cultures. Additionally, the electric current also reduced the degeneration of neurons within the original explanted ganglion, which usually occurs in culture systems. Later, growth promoting effects such as enhancement of number of neurite-bearing dissociated neurons in culture medium, the average neurite length, and the speed of neurite outgrowth were attributed to cathodal stimulation [5;6].

This procedure gained popularity when *in vivo* studies on adult rats supported that both DC and AC currents increased the innervation field of intact peripheral nerves [7]. Roman et al. later demonstrated that even though a transected rat sciatic nerve regenerated over a 5 mm gap on its own, electrical stimulation resulted in a larger neural bridge which was translated to larger number of myelinated and unmyelinated axons, as well as blood vessels compared to sham stimulus [8]. Also, in sutured axotomized rat femoral nerve, electrical stimulation enhanced the number of motonerurons that regenerated their axons through the site of anastomosis. Furthermore, this procedure markedly reduced the misdirection of motor axons towards the cutaneous sensory pathways, which is a major source of dysfunction and prolonged recovery after nerve severance [9].

The impact of electrical stimulation in augmenting functional recovery has also been demonstrated in crushed nerves. Animal studies have shown that toe spread reflex in rats, tetanic tension, twitch force, and muscle action potential in rabbits and canines returned to their pre-crush values sooner after electrical stimulation compared to controls [10-12]. Clinical applicability of electrical stimulation became even more promising when stimulations as brief as one hour proved to be as effective as longer stimulation periods [9].

Despite this body of evidence in favor of electrical stimulation as a nerve growth promoting intervention, its applicability in humans has never been tested. The aim of this study was to investigate the effectiveness of electrical stimulation on axonal regeneration in human subjects. Carpal tunnel syndrome (CTS) serves as an important model of nerve degeneration caused by sustained compression of the median nerve within the restricted anatomic boundaries of the carpal tunnel. Axonal degeneration has been shown to occur in the median nerve in moderate to severe CTS as demonstrated by absence or reduction of palmar sensory nerve action potential (SNAP) amplitude [13;14], enlarged motor units and decreased recruitment pattern in the thenar muscle on electromyography [15]. CTS is well suited to examine motor axonal regeneration for several reasons. First, the distance between the site of nerve injury and the target thenar muscles is relatively short so that reinnervation can be detected within a reasonably short time [9]. Second, open carpal tunnel release (OCTR) surgery is commonly used to treat CTS [16], therefore rendering the median nerve accessible for direct electrical stimulation. Moreover, the local anesthesia makes the subsequent electrical stimulation easily tolerable to the patients. Lastly, well established non-invasive methods for measuring motor axonal regeneration already exist for the thenar muscles [17].

We carried out this randomized controlled trial to test the hypothesis that 1-hour electrical stimulation of the median nerve with continuous 20 Hz stimulation after OCTR would accelerate regeneration of motoneuron axons and causes significantly better median motor reinnervation to the target muscles than conventional OCTR alone.

4.2 Methods:

This was a randomized controlled trial that complied with the guidelines of and was approved by the Human Research Ethics Board at the University of Alberta. All subjects gave their informed consent.

4.2.1 Subjects:

Subjects were recruited from a university hospital electromyography clinic. The inclusion criteria were presence of at least one of the following constellation of symptoms: (1) numbness and tingling in the median nerve distribution, (2) such sensory symptoms precipitated by repetitive hand activities and relieved by resting, rubbing, and shaking the hand, (3) nocturnal awakening by such sensory symptoms and (4) weakness of thumb abduction and thenar atrophy. Subsequently, the presence of median nerve compression was confirmed by electrophysiological studies. The exclusion criteria were presence of other neurological conditions, trauma to wrist or arm and previous carpal tunnel release. We looked for these factors through interviews and clinical examination. When indicated, further electrophysiologic studies and investigations were carried out. The ulnar nerve and the superficial radial nerve were evaluated through clinical examination and electrophysiological studies to rule out other peripheral neuropathies which may contribute to the hand symptoms.

4.2.2 Nerve Conduction Study:

All sensory and motor nerve conduction studies were performed on patients using a Viking Select EMG machine (Nicolet Biomedical, Minneapolis). Sensory and motor nerve conduction studies of the median nerve were done using standard techniques [18].

4.2.2.1 median sensory nerve conduction study:

The hand was cleansed with rubbing alcohol and the skin temperature was maintained 32 - 34 °C with an infrared lamp. Disposable silver/silver chloride surface strip electrodes (Nicolet VIASYS healthcare), measuring 1 x 2.5 cm, were used. The recording electrode was placed on the proximal interphalangeal joint and the reference electrode on the distal interphalangeal joint of the third digit. The median nerve was stimulated in mid palm and also just proximal to the distal wrist crease. The transcarpal sensory conduction velocity based on the onset latency, and the negative peak amplitude of the SNAP were measured.

4.2.2.2 median motor nerve conduction study:

The disposable recording surface strip electrode was placed over the motor point on the thenar eminence muscles and the reference electrode over the dorsal aspect of the first metacarpophalangeal joint. The median nerve was stimulated at supramaximal intensity at the wrist 8 cm proximal to the recording electrode and also at the elbow. The negative peak amplitude of maximal compound muscle action potential, terminal motor latency and conduction velocity in the forearm were measured.

In the current literature, the diagnosis of CTS and classification of its severity are commonly based on nerve conduction results [19]. In brief, patients with abnormal conduction velocity of the median sensory nerve fibers across the carpal tunnel but normal median terminal motor latency were classified as having mild CTS. If the conduction speed of the median sensory and motor nerve fibers were both abnormal but the action potentials were still present, the subjects were categorized as having moderate CTS. Lastly, if the median sensory nerve action potential was absent, the patients were classified as severe. Patients with moderate and severe CTS who had not responded to conservative treatments were recruited for this study.

4.2.3 Treatment Protocol:

Subjects were randomized to the control and the stimulation group by using the random number generation function in a commercially available software program (Excel, Microsoft Inc.). The control group underwent OCTR only. The stimulation group underwent OCTR followed by one hour of electrical stimulation of the median nerve.

4.2.3.1 surgical technique:

Operations were performed by a plastic surgeon (DE) in an outpatient surgical suite at the University of Alberta Hospital. The surgical procedure was the standard OCTR without epineurotomy or neurolysis of the median nerve [16]. A tourniquet was inflated over the forearm with the palm facing up. The surgeon drew a slightly curvilinear mark over the palm to guide the incision. Under local anesthesia, a 3 cm long longitudinal skin incision was made, extending from the distal wrist flexion crease along an axis on the radial side of the fourth digit. The transverse carpal ligament was dissected with a scalpel along the ulnar side of the incision. No further intervention was employed in the control group. For the stimulation group, two sterile 30 gauge wires (Cooner), insulted except the 1 cm at the tip, were placed over the median nerve. One electrode was positioned at the proximal end of the incision above and the other at the distal end of incision below the compression site. Since they needed to be removed after the stimulation, the wire electrodes were not fixed to the tissue. Each wire electrode was 30 cm in length to facilitate access to its free end for post surgical electrical stimulation. The skin margins were sutured together using 5-0 nylon. To record the compound muscle action potential (CMAP) during the post-surgical electrical stimulation, the surgeon placed two surface electrodes (TECA, Oxford Instruments), one over the motor point on the thenar eminence muscles and the other over the dorsal aspect of the first metacarpophalangeal joint. The tourniquet was deflated and the site was covered by a soft dressing (Fig. 4.1). Subjects were advised to keep their hands elevated above the heart level at most times for 48 hours after surgery to prevent subsequent hand swelling and discomfort. Finger movement and gentle use of hand after surgery was encouraged. The dressing was removed one week later and the sutures were removed two weeks after the surgery. Patients were allowed to return back to work 4-6 weeks after the surgery.

4.2.3.2 electrical stimulation:

Subjects in the stimulation group were transferred to a neurophysiology laboratory after OCTR. There was an approximately 30 minute delay between termination of OCTR and initiation of electrical stimulation. With the patient in the lying position, the operated hand was stabilized at an elevated position. The distal ends of the stimulating electrodes were connected to a Grass (SD9) stimulator: the proximal wire electrode was connected to the cathode and the distal one to the anode. The adhesive surface electrodes were connected to an EMG machine (NeuroSoft Inc., Virginia) to record the CMAP over the thenar muscles. We gradually increased the stimulation intensity to the maximal tolerance limit (4-6 V, 0.1-0.8 ms duration) as a continuous 20 Hz train for one hour. These frequency and duration parameters were selected based on previous studies [9]. However, animal studies had used supramaximal stimulation which could not be implemented on human subjects because of the associated discomfort. Stimulation induced contraction and the CMAP of the thenar muscles were also monitored. After the termination of stimulation, electrodes were pulled out and discarded.

4.2.4 Outcome Measures:

To compare the effectiveness of electrical stimulation with control OCTR, the subjects were evaluated twice before the operation (pre-op1 and pre-op2) to ensure reliability of the tests. Subjects were then followed up to one year at three time points after the OCTR. The follow-up schedule was: 1) post-op1; 3rd month, 2) post-op2; 6th to 8th months, and 3) post-op3; 12th month. The third month was selected for the first assessment based on the assumptions that the most optimal axons growth rate is 1 mm/day and the distance between the compression site and the thenar muscles is approximately 70 to 80 mm depending on the size of the hand. At each post operative assessment, all the baseline measures were repeated.

4.2.4.1 nerve conduction studies:

Median motor and sensory nerve conduction studies were carried out according to the same methods used for diagnosing CTS. The parameters assessed were the maximal CMAP negative peak amplitude, terminal motor latency, sensory nerve conduction velocity across the carpal tunnel and its negative peak amplitude.

4.2.4.2 motor unit number estimation (MUNE):

MUNE was performed on all patients using the multiple point stimulation technique to determine the number of motoneurons that regenerate their axons and innervate thenar muscles, as described by Doherty and Brown [20].

Recording: Disposable, self-adhesive surface electrodes (Nicolet, VIASYS), measuring 1 x 2.5 cm were used to detect the maximum M-wave and surface-detected motor unit action potential (S-MUAP). The reference electrode was positioned over the first metacarpophalangeal joint. The active electrode was placed over the innervation zone of the thenar muscles where the largest M-wave with the shortest rise time was obtained. A 3 x 3 cm metal plate was positioned on the back of the hand as a ground. The bandpass filter was set at 5-2000 Hz. The position of the thumb was standardized by taping it to the side of the palm in an adducted position.

Stimulation: Electrical stimulation of the nerve was performed with a hand-held constant-current bipolar surface bar stimulator. The maximum M-wave of the median nerve was evoked by stimulating the median nerve at the wrist at 10 % above the maximal intensity with a duration of 0.01 ms. The course of the median nerve was mapped from the elbow to the axilla by advancing the bar stimulator over the medial aspect of the arm at 1-2 cm intervals. Because the median and ulnar nerves are in close proximity in the upper arm, it was necessary to avoid co-stimulation of the ulnar nerve while mapping the course of the median nerve. Co-activation of the ulnar nerve was recognized by (1) an initial positive deflection of the M-wave, (2) abduction of the fifth digit, and (3) the radiation of an electrical sensation into the fourth and fifth digits. In earlier experiments, we also co-recorded from the hypothenar eminence and found that when the above conditions were avoided, there was no detectable action potential generated by the hypothenar muscles.

Using the same recording electrodes, S-MUAPs with the lowest stimulus thresholds were elicited by stimulating the median nerve at multiple sites at the wrist and between the elbow and the axilla. Stimulation was performed at 1 Hz with gradually increasing intensity until the first reproducible, "all-or-none" S-MUAP was evoked. Using the template subtraction method, the lowest threshold S-MUAP was obtained by subtracting the "all" response from the baseline. To increase the yield, the next higher threshold S-MUAP could sometimes be obtained through template subtraction. A collected sample of at least 12 S-MUAPs was stored in computer memory. The mean peak-to-peak amplitude of this sample of S-MUAPs was calculated using "datapoint-by-datapoint" summation. All S-MAUPs were temporally aligned at the same onset latency before they were averaged. The motor unit number estimate was obtained using the following equation:

$$\frac{\text{Peak-to-peak amplitude of the maximum M-wave}}{\text{Peak-to-peak amplitude of the average S-MUAP}}$$

4.2.4.3 Levine's Self-Assessment Questionnaire for CTS:

To assess the subjective symptoms, patients were asked to complete the Levine's Self-Assessment Questionnaire for CTS symptom severity [21]. This questionnaire has been shown to be more sensitive than other questionnaires such as the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire and the 36-item Short-Form Health Survey (SF-36) [22].

The Levine's Self-Assessment Questionnaire consisted of two parts: 1) symptom severity scale comprised of 11 items scored on a Likert scale inquiring about pain, paraesthesia, numbness, weakness, nocturnal symptoms and overall functional status, and 2) functional status scale comprised of eight questions regarding activities of daily life commonly affected by CTS. The symptom severity scores ranged from 1 to 5 with 1 representing no symptoms and 5, very severe symptoms. The functional status scores also ranged from 1: no difficulty to do a task, to 5: inability to do a task (Appendix 1). The total score on this questionnaire was used to assign CTS severity.

4.2.4.4 The Purdue Pegboard Test:

We used the Purdue Pegboard Test to monitor the impact of treatments on manual dexterity. The Purdue Pegboard Test is a standardized hand function tool with proven validity and reliability in the functional evaluation of CTS patients [23].

The Purdue Pegboard Test (Model 32020, Lafayette Instrument Company, IN, USA) consisted of 50 holes arranged in two parallel columns and pegs, washers, and collars located in four cups at the top of the board. The pegs were placed in cups on the far right and far left of the board so that they could be conveniently reached by both hands. The pegboard was located on a table crosswise, and subjects sat comfortably in front of it. Subjects were instructed to start the test on a verbal cue, while an examiner timed the test with a stopwatch. Subjects had 30 s to fill the holes with pegs initially with the hand intended for surgery and then with the other hand. Each subset was repeated three times to obtain an average. Test scores equaled the number of filled holes which were used as the determinant of manual dexterity. The Purdue Pegboard Test has two additional subsets which are performed bimanually.

However, that did not apply to this study since we intended to compare the function of the treated and non-treated hands separately.

4.2.4.5 Semmes Weinstein Monofilaments (SWM):

As sensory complaints are prominent in CTS, we used a test kit of 20 SWM (Sammons Preston Rolyan-Canada) to assess the impact of treatments on hand sensation. This tool, which examines the sensation threshold, has proven reliability [24] and is utilized in the clinical evaluation of peripheral nerve diseases such as diabetic neuropathy [25;26].

We employed the standard methods for SWM [27]. Briefly, subjects were asked to place their hands over a table, and keep their eyes closed for the duration of this test. Each filament, starting with the smallest caliber, was tested over the pulp of digits. The filament was applied perpendicularly for 1 to 1.5 seconds in three trials. Subjects were asked to indicate the area where the filament was felt. A positive response in at least one of the three trials marked the sensory threshold. If subjects failed to feel a filament, filaments with the next higher caliber were employed until a positive response was found. We examined the sensory threshold of all fingers in random order. We used the test results of the third digit where sensory nerve conduction study was also done, for data analysis.

4.2.5 Statistical Analysis:

The statistical program SPSS 12.0 for Windows was used in this study. Using the Shapiro-Wilk Test of normality, we found that nerve conduction studies, and SWM results were significantly skewed from a gaussian distribution ($p<0.05$), making non-parametric methods appropriate for their analysis. Additionally, the Mauchley's test of sphericity was statistically significant ($p<0.05$) when using repeated ANOVA to analyze the Levine's Self-Assessment scores, the Purdue Pegboard test, and MUNE, rendering parametric tests unsuitable. Therefore, we used Kendall's W and Wilcoxon Signed Ranks test to compare all the outcome measures within each group of subjects. To examine whether the preoperative outcome measure values were significantly different between the two groups, the Kruskal-Wallis test was employed. The statistical significance was set at $p<0.05$.

4.3 Results:

4.3.1 Subjects:

Twenty four eligible subjects participated in the study, all of whom underwent surgical decompression. However, 4 subjects (2 male and 2 female) withdrew from the study because of development of other medical conditions, or occupational commitments which prevented them to return for follow up. Two of these patients belonged to the control and 2 to the stimulation group. Therefore, the results came from 20 subjects: 8 male and 12 female. They were from 20 to 86 years old, with an average age of 56±17 (Mean±SD). Their occupations ranged from housewives, nurses, medical and laboratory technicians, cooks, manual laborers, and retirees.

Eighteen subjects were right hand dominant (defined as the hand used for writing). Clinical investigations and nerve conduction studies confirmed bilateral CTS in 18 subjects. The dominant hand in 18 subjects had more severe CTS and subsequently was operated. However, 5 patients later also had the surgery done on their other hand, thus both hands were included in the study. Subsequently, the data belonging to 24 hands were used for analysis.

Nine patients were assigned to the control group and 11 patients to the stimulation group. All subjects attended the first post-op follow-up, whereas 17 of them were available for the second post-op evaluation. Two of the subjects who missed the appointment belonged to the control and 1 to the stimulation group. Thirteen patients completed the third follow up: 7 in the control and 6 in the stimulation group.

4.3.2 Outcomes:

4.3.2.1 nerve conduction studies:

a) median motor conduction studies:

The maximum normal limit of terminal motor latency for median nerve is 4.2 ms [18]. The baseline median value of terminal motor latency was 5 ms for the control group and 5.7 ms for the stimulation group. This value was not significantly different between the treatment and the control group ($p=0.15$).

The stimulation group demonstrated significant improvement of terminal motor latency in post-op1, post-op2, and post-op3 assessments ($p<0.05$). The median value of this parameter reached 4 ms one year after surgery in both groups. In contrast, this improvement was not statistically significant in the control group ($p>0.1$) (Fig. 4.2).

The CMAP amplitude had a wide variability in the control group, with a median of 10 mV. Although by post-op2 and post-op3 those abnormal CMAP amplitudes had normalized, the control group collectively did not show a significant improvement in any of the post-op assessments ($p>0.4$). The preoperative median CMAP amplitude was slightly lower in the stimulation group (8 mV) than controls (10 mV). However, this difference was not statistically significant ($p=0.38$). The CMAP amplitude in the stimulation group remained similar throughout the follow-ups ($p>0.2$) (Fig. 4.2).

b) median sensory conduction studies:

The minimum cut off for normal median sensory conduction velocity across the carpal tunnel was 50 m/s [18]. The median sensory conduction velocity was 28 m/s in controls and 25 m/s in stimulation group preoperatively ($p=0.7$). After the operation, the stimulation group demonstrated a significant improvement in sensory conduction velocity detectable as early as post-op1. Their median value of sensory conduction velocity reached 35 m/s by post-op1, 38 m/s by post-op2 and 41 m/s by post-op3, all were statistically significant ($p<0.05$). Although the control subjects also experienced a significant improvement in their conduction velocity, this was delayed compared to the stimulated subjects. The control group attained a median sensory conduction velocity of 31 m/s by post-op1 ($p=0.26$), 36 m/s by post-op2 ($p<0.01$), and 40 m/s by post-op3 ($p<0.05$) (Fig. 4.3).

All subjects had sensory nerve action potential (SNAP) amplitudes below the normal level; it was even undetectable in some cases. The median SNAP amplitude was 4 μA in the stimulation group and 8 μA in controls preoperatively. However, this difference between the preoperative values of the two groups was not statistically significant ($p=0.66$). After the operation, this value progressively increased in both groups. However, this improvement was again further accelerated in the stimulated subjects, even though their baseline median SNAP amplitude was 50% smaller than controls. In the stimulation group, this value doubled by post-op2 reaching 8 μA ($p<0.01$), and quadrupled by post-op3 reaching 12 μA ($p<0.05$). Conversely, significant improvement did not occur in the control group until one year after OCTR. They reached a median value of 9 and 13 μA by post-op2 ($p=0.11$) and post-op3 ($p<0.05$) respectively. There was no significant change in the SNAP amplitude by post-op1 in either group ($p>0.1$) (Fig. 4.3).

4.3.2.2 motor unit number estimation (MUNE):

Using the multiple point stimulation technique, Doherty and Brown have shown that the average MUNE in the thenar muscle of healthy subjects is 288 [28].

In our study, subjects had a preoperative mean MUNE of 163 and 146 in the stimulation and control group respectively, which was substantially lower than healthy subjects. The range of MUNE for the stimulation group was 74 to 243, and for the control group was 21 to 230. There was no significant difference between the MUNE values at pre-op1 and pre-op2 in both groups ($p>0.3$), indicating the reliability of this parameter. Subsequently, post-op MUNEs were compared with pre-op1 values for follow-up.

In the stimulation group, the mean MUNE reached 219 by post-op1 which was statistically comparable to its pre-op value ($p=0.11$). However, by post-op2 these subjects demonstrated a significant rise in their mean MUNE to 238 ($p<0.05$). The improvement in MUNE further progressed by post-op3 to a mean value of 266, with a range of 122 to 550 ($p<0.05$) (Fig. 4.4).

Contrary to the stimulation group, we did not detect any significant increase in the MUNE of the control group even by post-op3 ($p>0.2$). The mean MUNE was 154 by post-op1, 163 by post-op2, and 216 by post-op3.

4.3.2.3 Levine's Self-Assessment Questionnaire:

The score for subjects with no hand symptoms on the Levine's Self-Assessment Questionnaire is 19. As the severity of CTS increases, Levine's symptom severity score also increases. The maximum score is 95 in very severe cases.

The median score for subjects in this study was 52 for the stimulation group and 60 for controls preoperatively. The most severe scores were 58 and 74 in the stimulation and control group respectively. The range of symptom severity was wider for the control group. The subjective symptom severity scores in pre-op2 concurred with pre-op1 scores in both groups ($p>0.08$). After surgery, significant relief of symptoms was reported by the subjects in both groups as early as post-op1 and was maintained in post-op2 and 3 ($p<0.05$). The median post-op score was 30 or less for both groups. Of note, subjects who reported to be completely symptom free at post-op2 and 3 all belonged to the stimulation group (Fig. 4.5).

4.3.2.4 The Purdue Pegboard Test:

Manual dexterity of the subjects in performing the Purdue Pegboard Test was reflected by the number of holes they could fill during a 30 s interval. As the manual dexterity declines, subjects score less on the number of holes that could be filled. The average normal score is 17 with an overall range of 13 to 19 pegs [29].

Subjects in the control and stimulation group had a median score of 11 and 12 respectively at pre-op1 and the overall pre-op range varied from 3 to 17 pegs. The performance of subjects at pre-op2 was comparable to pre-op1 in both groups ($p>0.2$) (Fig. 4.6).

Performance of the operated hand on the Purdue Pegboard Test significantly improved by post-op1, 2, and 3 in both groups ($p<0.05$). Although the median number of manipulated pegs did not go beyond 14, the range improved to a minimum of 8 and a maximum of 18 especially by post-op2 and 3.

To ensure that this improvement in manual dexterity was the result of treatment as opposed to practice effect, we also examined the hand function of the non-operated hand. The median number of pegs manipulated by the non-operated hand was 13 and 12 in the control and stimulation group respectively, with an overall range of 5 to 18. The manual dexterity of the control hand in both groups did not demonstrate any significant improvement during follow-ups ($p>0.1$) (Fig. 4.6).

4.3.2.5 Semmes Weinstein Monofilaments:

Each monofilament of the Semmes Weinstein kit is calibrated to apply a certain pressure per cm^2 surface area of the skin. The first 4 filaments represent the normal threshold of sensory perception (4.5—67.7 mg/cm^2), filaments 5 and 6 represent diminished light touch (166—408.2 mg/cm^2), and filaments 7 to 10 represent diminished protective sensation (695.8—2052 mg/cm^2). The last 10 filaments represent loss of protective sensation (3632—447000 mg/cm^2).

The median pressure perceived over the third digit preoperatively was 68 mg/cm^2 for the stimulation group and 48 mg/cm^2 for the control group, which was still within the normal range. However, some subjects in the stimulation group had a sensory threshold as high as 1200 mg/cm^2 indicating diminished protective touch.

The maximum sensory threshold for the control group was noticeably higher with a value of 29000 mg/cm^2, indicating that some subjects had lost protective sensation. Sensory thresholds in pre-op1 and pre-op2 were comparable ($p>0.2$).

After the operation, the median sensory threshold decreased to 28 mg/cm^2, 16 mg/cm^2, and 4.5 mg/cm^2 by post-op1, 2, and 3 respectively in the stimulation group, reaching the lowest normal sensory threshold after one year. This improvement in sensation was statistically significant ($p<0.05$) in post-op2 and 3 ($p=0.1$ for post-op1). The control group also experienced a significant reduction in the threshold for sensation, achieving a median value of 28 mg/cm^2 in post-op1, 2, and 3 ($p<0.05$) (Fig. 4.7).

4.4 Discussion:

This study demonstrated that electrical stimulation following decompression surgery of carpal tunnel syndrome patients resulted in a surge in axonal regeneration, represented by a significant rise in MUNE at post-op2 and 3. On the contrary, the OCTR alone was not sufficient to cause significant improvement in axonal regeneration even one year after the operation, as the MUNE did not significantly improve in controls. This finding concurs with our hypothesis that electrical stimulation augments axonal regeneration.

Although this effect was previously shown in animal studies, this is the first human study that confirmed similar enhancement of axonal regeneration in patients with nerve compression.

Nerve conduction studies provided further supplementary information. The sensory nerve conduction studies showed a significant increase in the transcarpal sensory conduction velocity and palmar SNAP amplitude in both groups. However, the electrical stimulation had hastened this effect so that it appeared earlier compared to controls. The motor nerve conduction studies further affirmed the positive impact of electrical stimulation: the significant improvement in the terminal motor latency of the median nerve occurred earlier in the stimulation group and was detectable as early as post-op1. These findings suggest that electrical stimulation may particularly affect the regeneration of large fiber axons with fast conduction.

Results of the Semmes Weinstein Monofilaments and the Purdue Pegboard Test revealed a significant clinical recovery in both groups. Sensory threshold of the median-innervated digit had markedly improved and attained normal values. This improvement did not achieve statistical significance at post-op1 in the stimulation group perhaps because of less preoperative sensory impairment compared to the control group.

The Levine's Self-Assessment Questionnaire also showed a significant recovery following surgery in both groups. This outcome is in agreement with other reports on the efficacy of OCTR, using subjective tools [30]. This finding was expected since the neurophysiologic basis for improvement in subjective symptoms is quite different from that of axonal regeneration.

Our result is in agreement with the work of Al-Majed et al. on axotomized rat femoral nerve [9]. They employed backlabeling methods with neurotracers and showed that electrical stimulation increases the number of motoneurons that regenerate their axons through the lesion and innervate the target muscle. Electrical stimulation exerts its effect on axonal regeneration via the motoneuron cell body, because the blockade of retrograde transmission of action potentials to the cell body by tetrodotoxin abolishes the positive effect of electrical stimulation [9]. This implies that electrical stimulation up-regulates the substrates involved in nerve growth promotion that are controlled via the cell body. One of the possible players is brain derived neurotrophic factor (BDNF). This neurotrophin is normally detected at low concentrations in intact nerves, and increases after axotomy [31]. The expression of BDNF mRNA and its receptor (TrkB) increase in the motoneurons of axotomized nerves after electrical stimulation [32]. Therefore, BDNF may contribute to the positive effect of this intervention. Other possible players which are influenced by electrical stimulation include Tα1-tubulin, GAP 43 and the medium-molecular-weight neurofilament (NFM), which are regulated in concert with BDNF and its receptor. Following 1-hour stimulation of axotomized femoral nerves in rats, the mRNA levels of Tα1-tubulin and GAP 43 increases at an accelerated pace in motoneurons while the NFM mRNA decreases [33]. This matches the role of these factors in nerve regeneration: simultaneous up-regulation of tubulin and down-regulation of NFM gene expression allows faster transport of tubulin and subsequently axonal regeneration [34]. Also, GAP 43 is involved in spontaneous sprouting of neurons [35]. Therefore, it seems that electrical stimulation may initiate a cascade of nerve growth promoting events.

By employing a constellation of outcome measure tools in this study, we conclude that 1-hour electrical stimulation of the median nerve after surgical decompression significantly increases the axonal regeneration. This is supported by a marked increase in the number of motoneurons that develop nerve-muscle connections. This procedure was proven feasible in the clinical setting. Additionally, patients did not develop any complications due to surgery or the stimulation.

We believe the lack of blinding in this study likely did not affect the results. The Levine's Self-Assessment Questionnaire for CTS was the only subjective outcome measure which had the potential to be biased by patients' knowledge about the treatment. However, in this study both the stimulation and control groups showed a significant improvement in their symptom severity by post-op1. The other outcome measure tools such as nerve conduction studies and the MUNE are objective measures that cannot be easily influenced by the subject or the examiner.

To better understand the functional outcomes of electrical stimulation, in future studies other outcome measures such as grip strength, maximum voluntary contraction, and tetanic tension of the target muscle should also be employed. Based on previous animal studies, we used 1-hour stimulation. In future studies, attempts could be made to reduce the duration of electrical stimulation further.

The present study sets the stage for further human studies to extend the applicability of this procedure to other clinical scenarios. In addition to carpal tunnel syndrome, our findings may also be applicable to other nerve injuries with preserved continuity of neural conduit where the distance between the nerve lesion and the target muscles is short, for example, compression of the ulnar nerve in Guyon's canal [36]. The increase in the speed of regeneration may be particularly crucial in other instances such as entrapment of the ulnar nerve at the elbow or within the Arcade of

Struthers at the upper arm where the axons need to regenerate over a much longer distance. Lastly, post surgical electrical stimulation may also benefit transected nerve injuries. Lundborg et al. reported motor and sensory recovery in transected median nerve after the proximal and distal nerve stumps were approximated by a silicone chamber [37], but the recovery took 3 years. It is possible that additional electrical stimulation can expedite the functional outcome of these procedures.

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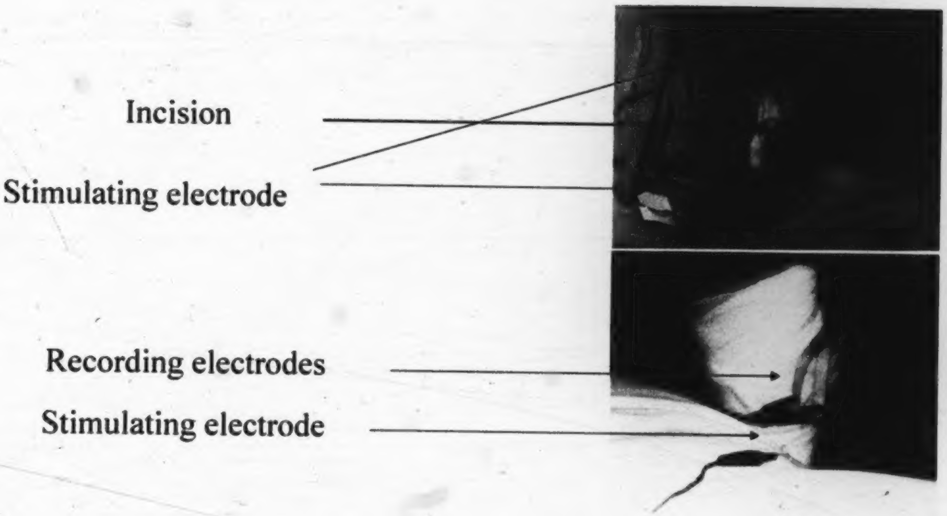
Incision
Stimulating electrode
Recording electrodes
Stimulating electrode

Figure 4.1. Experiment set up.
Top figure: presentation of stimulating electrodes after termination of surgery. Bottom figure: presentation of stimulating and recording electrodes during electrical stimulation.

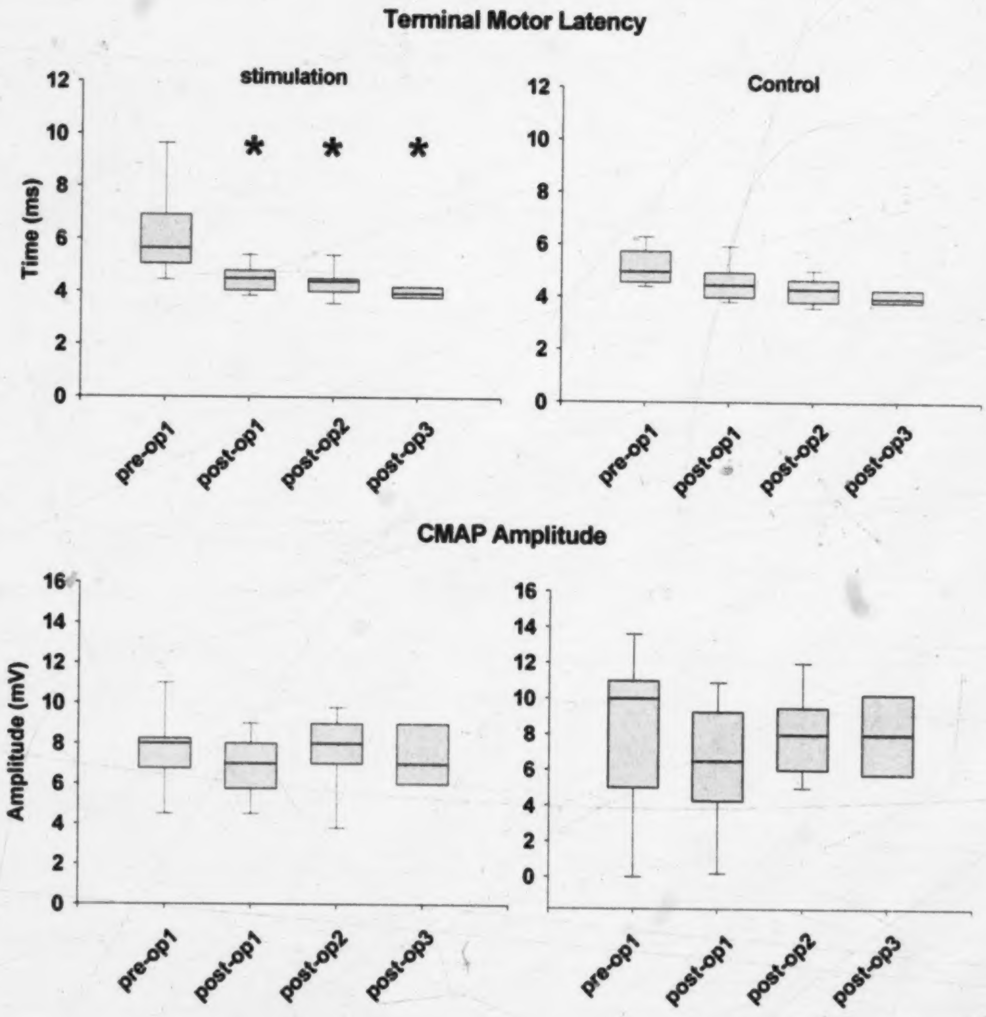

Figure 4.2. Motor nerve conduction studies.
Box plots represent the median (middle line), 75th and 25th percentile (upper and lower margins of the box plot). Upper and lower whiskers represent 90th and 10th percentiles respectively. Black dots show the entire range. Absence of whiskers means that all values are within 25th-75th percentile range * denotes $p<0.05$.

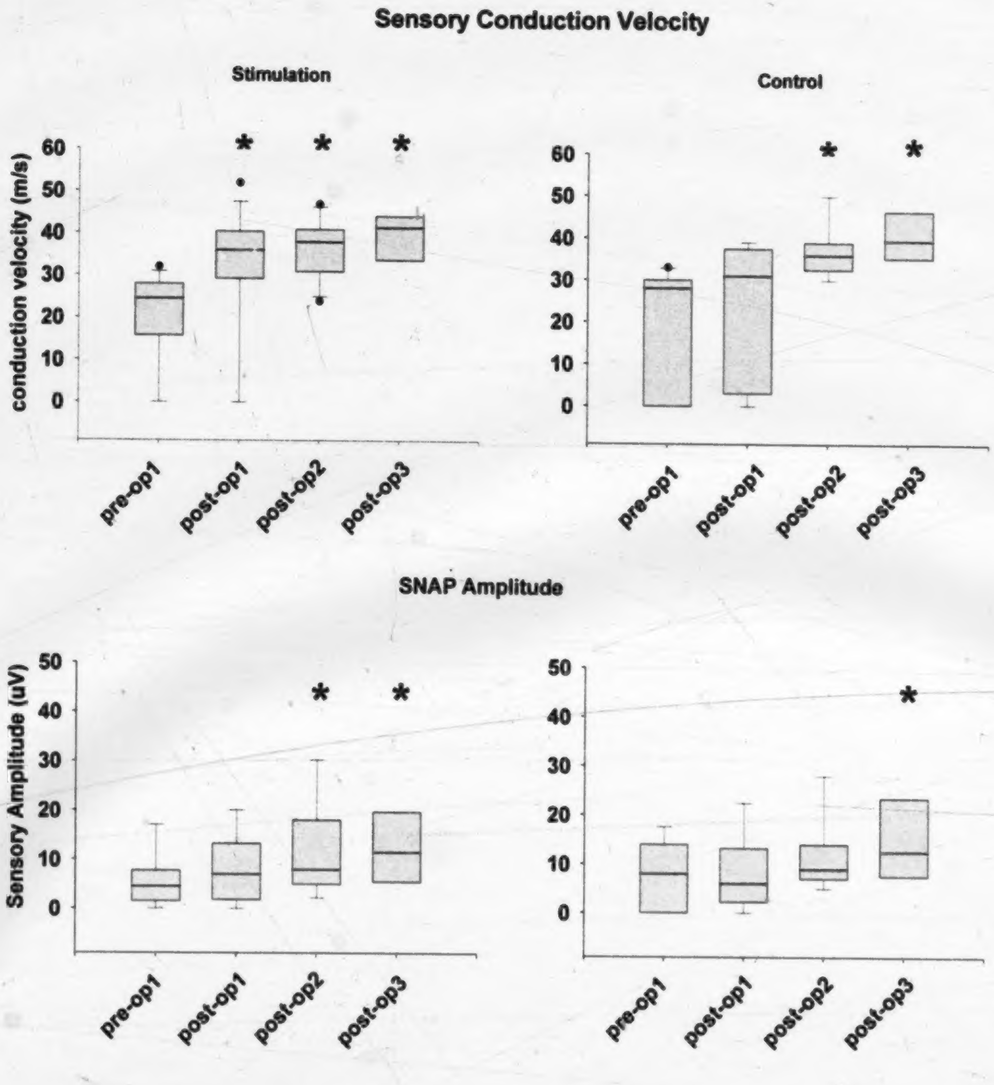

Figure 4.3. Sensory nerve conduction studies.
Box plots represent the median (middle line), 75th and 25th percentile (upper and lower margins of the box plot). Upper and lower whiskers represent 90th and 10th percentiles respectively. Black dots show the entire range. Absence of whiskers means that all values are within 25th-75th percentile range * denotes $p<0.05$.

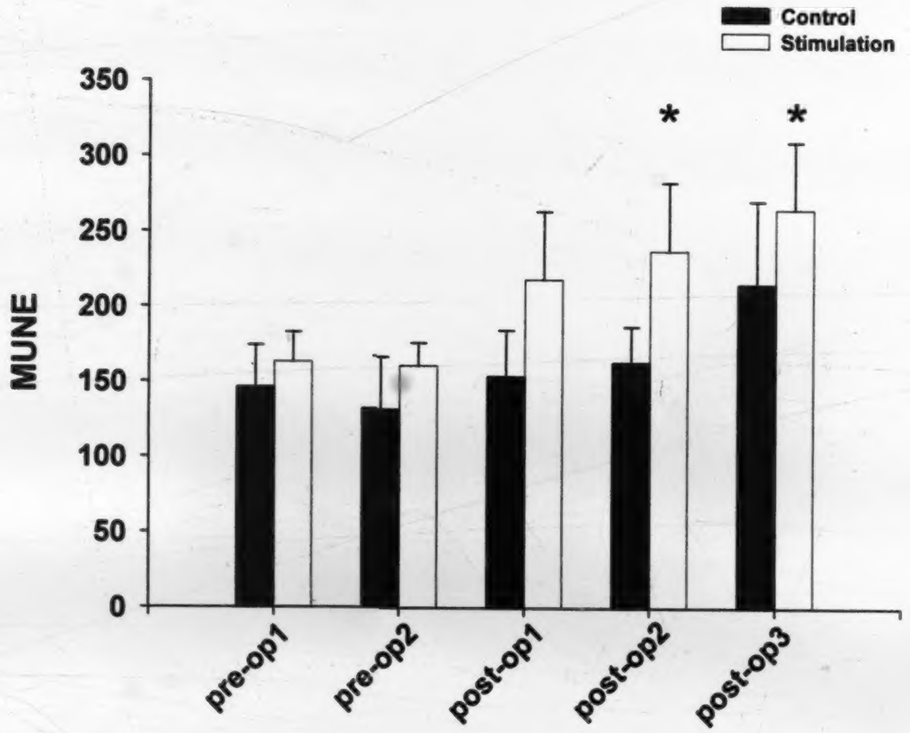

Figure 4.4. Comparison of MUNE in the stimulation and control group.
Plots represent mean±SE, * denotes $p<0.05$ in comparison with pre-op1. Normal MUNE is 288±95.

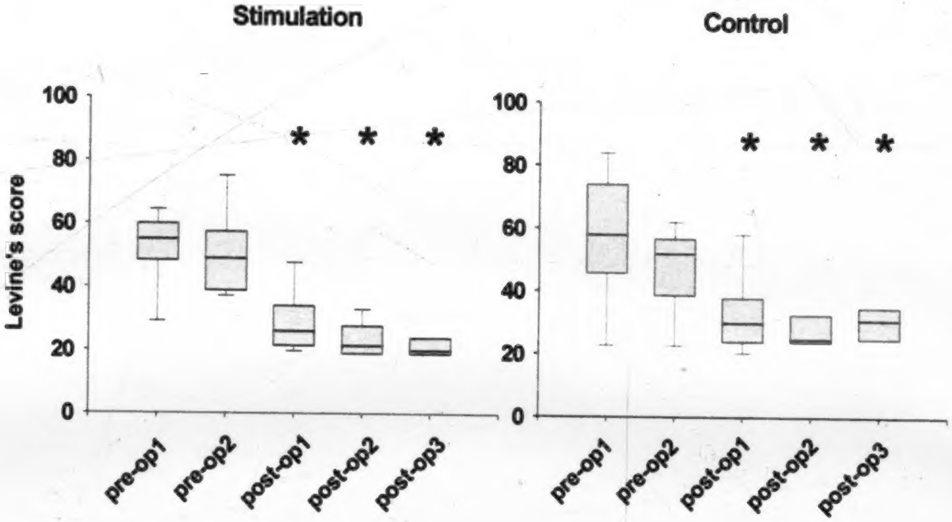

Figure 4.5.Comparison of Levine's Self Assessment Questionnaire.
Box plots represent the median (middle line), 75th and 25th percentile (upper and lower margins of the box plot). Upper and lower whiskers represent 90th and 10th percentiles respectively. Black dots show the entire range. Absence of whiskers means that all values are within 25th-75th percentile range * denotes $p<0.05$.

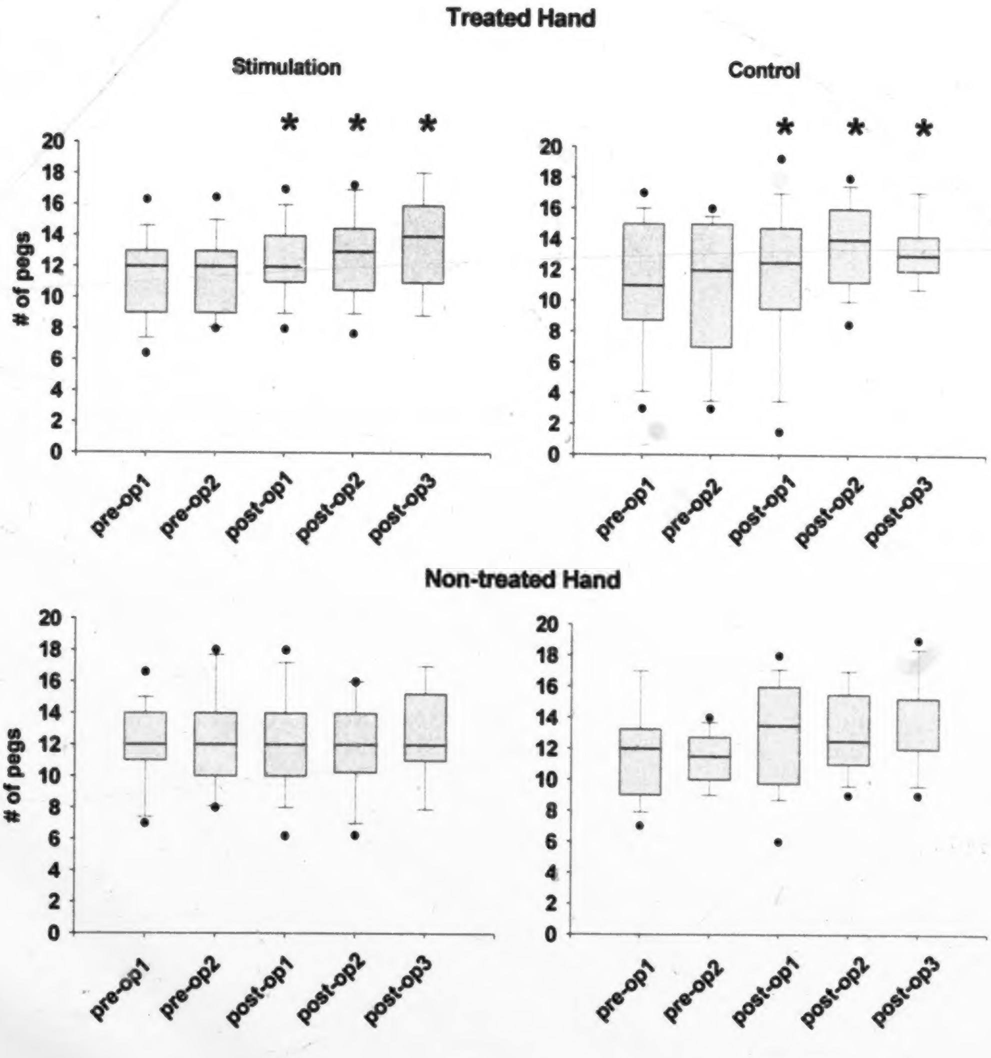

Figure 4.6. Comparison of the Purdue Pegboard Test.
Box plots represent the median (middle line), 75th and 25th percentile (upper and lower margins of the box plot). Upper and lower whiskers represent 90th and 10th percentiles respectively. Black dots show the entire range. Absence of the middle line in post-op3 of the non-treated hand in control group is due to its overlap with the 25th percentile. * denotes $p<0.05$.

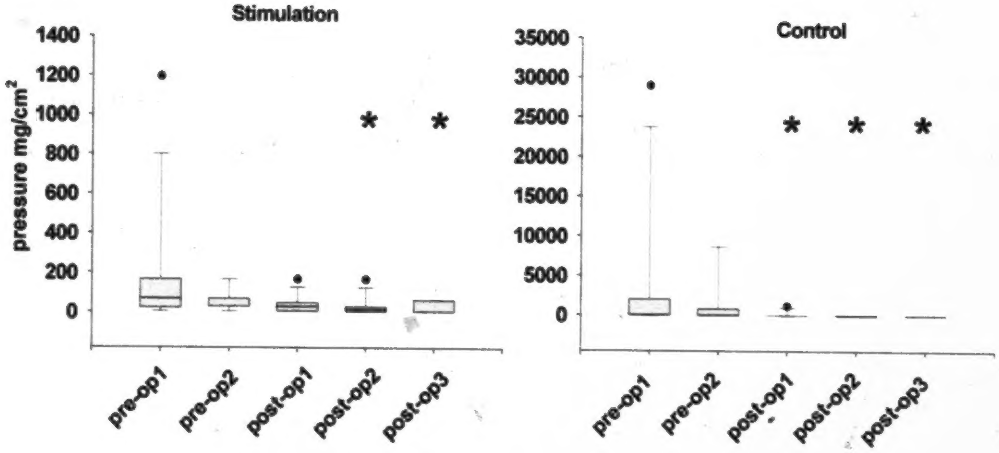

Figure 4.7. Comparison of Semmes Weinstein Monofilaments.
Box plots represent the median (middle line), 75th and 25th percentile (upper and lower margins of the box plot). Upper and lower whiskers represent 90th and 10th percentiles respectively. Black dots show the entire range. Due to lack of enough variability some of the 10th percentile whiskers are absent. Also in the control group the range had narrowed in post-op assessments. The middle line has overlapped with the 25th percentile in post-op3 of stimulation group. * denotes $p<0.05$.

Chapter 5

Corticosteroid Iontophoresis is not an Effective Treatment for Carpal Tunnel Syndrome

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5.1 Introduction:

Compression of a peripheral nerve triggers a chain of inflammatory reactions including increased permeability of endoneurial capillaries, edema, recruitment of macrophages, and endoneurial fibrosis [1;2]. Reduction of the inflammatory cascade by application of anti-inflammatory agents such as corticosteroids diminishes the ensuing nerve injury. For instance, Hong et al. demonstrated that local compression of the rat caudal nerve causes a conduction block that can be alleviated by local administration of dexamethasone [3]. This effect is thought to be through attenuation of macrophage recruitment to the area of nerve injury [4]. Sekiya et al. observed that compression of the myelinated segment of the cochlear nerve caused less nerve damage and retrograde degeneration of spiral ganglion cells in those rats which were injected with methylprednisolone than the control group. This effect corresponded with a significant reduction in macrophages invading the lesion site. Similar observations were also made in the spinal cord when administration of corticosteroids decreased the influx of macrophages to the lesion area resulting in less severe nerve damage [5;6]. It appears that methylprednisolone lowers the local concentration of TNF-α and IL-1 that are involved in macrophage recruitment and proliferation [7-9]. Glucocorticoids are also known to decrease IL-1, 2 and 3, and gamma interferon production, thus reducing secretion of cytotoxins by macrophages [10].

Carpal tunnel syndrome (CTS) is a common compressive neuropathy that benefits from corticosteroid injection as a therapeutic intervention [11]. In a recent study, local injection of 40 mg methylprednisolone acetate into the carpal tunnel in mild CTS significantly reduced the symptoms for at least 16 months in almost 80% of patients, and normalized the electrophysiologic parameters in 50% of subjects by 12 months after the treatment [12]. Additionally, Ly-Pen et al. demonstrated that 1 year after the treatment, local corticosteroid injection is as effective as decompression surgery in relieving the symptoms [13].

Despite the abundant evidence to support the effectiveness of steroid administration in ameliorating the symptoms of nerve compression, its use by injection has never gained popularity due to several reasons. First, the procedure is invasive particularly when aimed at a part of the hand that is highly sensitive. Second, given the confined space that the median nerve and the flexor tendons occupy within the carpal tunnel, there is a risk of accidental damage to those structures by the advancing needle tip and the injected bolus. Third, these risks are cumulative with repeated injections, making further treatment even riskier [1]. Therefore, a less invasive and safer method of drug delivery is much needed.

For these reasons, transcutaneous application of corticosteroids over the carpal tunnel is preferred. Indeed, it has been convincingly shown in animal studies that the skin has the ability to take up drugs. However, the depth of penetration greatly depends on the lipophilicity of the solution [14;15], thus limiting the efficacy of topical application of corticosteroids which are hydrophilic. Fortunately, iontophoresis electrolyses hydrophilic drugs such as dexamethasone to their ionized forms, which readily penetrate through the skin to deeper subcutaneous structures [16]. Therefore, iontophoresis appears to be an appealing alternative in delivering corticosteroids to the carpal tunnel. We carried out the present study to determine: 1) the effectiveness of corticosteroid iontophoresis in relieving CTS manifestations in mild and moderate cases, compared to the placebo treatment, and 2) the duration of the efficacy of this treatment.

5.2 Methods:

This was a double-blind randomized controlled trial that complied with the guidelines of and approved by the Human Research Ethics Board at the University of Alberta. All subjects gave their informed consent.

5.2.1 Subjects:

Subjects were recruited from a university hospital electromyography clinic. The inclusion criteria were presence of at least one of the following constellation of symptoms: (1) numbness and tingling in the median nerve distribution, (2) sensory symptoms were precipitated by repetitive hand activities and relieved by resting, rubbing, and shaking the hand, and (3) nocturnal awakening by the hand symptoms. Subsequently, the presence of median nerve compression was confirmed by electrophysiological studies. The exclusion criteria were presence of thenar atrophy, previous carpal tunnel release, previous corticosteroid injection into the carpal tunnel, other neurological conditions, and trauma to wrist or arm. We searched for these factors through interview and clinical examination. When indicated, further electrophysiologic studies and investigations were carried out. The ulnar nerve and the superficial radial nerve were also evaluated through clinical examination and electrophysiological studies to rule out other peripheral neuropathies which may contribute to the hand symptoms.

5.2.2 Nerve Conduction Study:

All sensory and motor nerve conduction studies were performed on patients using a Viking Select EMG machine (Nicolet Biomedical, Minneapolis, MN, USA). Sensory and motor nerve conduction studies of the median nerve were done using standard techniques [17]:

5.2.2.1 median sensory nerve conduction study:

The hand was cleansed with rubbing alcohol and its temperature was maintained between 32 and 34 °C with an infrared lamp. Disposable silver/silver chloride surface strip electrodes (Nicolet VIASYS Healthcare), measuring 1 x 2.5 cm, were used. The reference electrode was placed on the distal interphalangeal joint and the recording electrode on the proximal interphalangeal joint of the third digit. The median nerve was stimulated in mid palm and also just proximal to the distal wrist crease. The conduction velocity of the sensory nerve action potential across the carpal tunnel and its amplitude were measured.

5.2.2.2 median motor nerve conduction study:

The disposable recording surface strip electrode was placed over the motor point on the thenar eminence muscles and the reference electrode over the dorsal aspect of the first metacarpophalangeal joint. The median nerve was stimulated at supramaximal intensity at the wrist 8 cm proximal to the recording electrode and also at the elbow. The maximal compound muscle action potential amplitude, terminal motor latency and conduction velocity in the forearm were measured.

The diagnosis of CTS and its severity was substantiated based on the nerve conduction values that are commonly used in the literature [18]. In brief, patients with abnormal conduction velocity of the median sensory nerve fibers across the carpal tunnel but normal median terminal motor latency were classified as having mild CTS. If the conduction speed of the median sensory and motor nerve fibers were abnormal but the action potentials were still present, the subjects were categorized as having moderate CTS. Lastly, if the median sensory nerve action potential was absent, the patients were classified as severe.

Patients with mild to moderate CTS were recruited for this study.

5.2.3 Motor Unit Number Estimation (MUNE):

Since patients with severe CTS likely already have substantial axonal loss, mild to moderately affected subjects are more likely to experience alleviation of symptoms following conservative treatments. To rule out substantial axonal degeneration we carried out MUNE on subjects who met the eligibility criteria. Subjects with at least 120 motor units in their median innervated thenar muscles were deemed suitable candidates for this study [19]. The method used to do MUNE was the same as that originally described by Doherty and Brown [20]:

Recording: Disposable, self-adhesive surface electrode (Nicolet, VIASYS healthcare), measuring 1 x 2.5 cm was used to detect the maximum M-wave and surface-detected motor unit action potential (S-MUAP). The reference electrode was positioned over the first metacarpophalangeal joint. The active electrode was placed over the innervation zone of the thenar muscles where the largest M-wave with the shortest rise time was obtained. A 3 x 3 cm metal plate was positioned on the back of the hand as a ground. The bandpass filter was set at 5-2000 Hz. The position of the thumb was standardized by taping it to the side of the palm in an adducted position.

Stimulation: Electrical stimulation of the nerve was performed with a hand-held constant-current bipolar surface bar stimulator. The maximum M-wave of the median nerve was evoked by stimulating the median nerve at the wrist at 10 % above the maximal intensity with a duration of 0.01 ms. The course of the median nerve was mapped from the elbow to the axilla by advancing the bar stimulator over the medial aspect of the arm at 1-2 cm intervals. Because the median and ulnar nerves are in close proximity in the upper arm, it was necessary to avoid co-stimulation of the ulnar nerve while mapping the course of the median nerve. Co-activation of the ulnar nerve was recognized by (1) an initial positive deflection of the M-wave, (2) abduction of the fifth digit, and (3) the radiation of an electrical sensation into the fourth and fifth digits. In earlier experiments, we also co-recorded from the hypothenar eminence and found that when the above conditions were avoided, there was no detectable action potential generated by the hypothenar muscles.

Using the same recording electrodes, S-MUAPs with the lowest stimulus thresholds were elicited by stimulating the median nerve at multiple sites at the wrist and in the upper arm between the elbow and the axilla. Stimulation was performed at 1 Hz with gradually increasing intensity until the first reproducible, "all-or-none" S-MUAP was evoked. Using the template subtraction method, the lowest threshold S-MUAP was obtained by subtracting the "all" response from the baseline. To increase the yield, the higher threshold S-MUAPs could sometimes be obtained through template subtraction. A collected sample of at least 12 S-MUAPs was stored in computer memory. The mean peak-to-peak amplitude of this sample of S-MUAPs was calculated using "datapoint-by-datapoint" summation. All S-MAUPs were temporally aligned at the same onset latency before they were averaged. The motor unit number estimate was obtained using the following equation:

$$\frac{\text{Peak-to-peak amplitude of the maximum M-wave}}{\text{Peak-to-peak amplitude of the average S-MUAP}}$$

5.2.4 Treatment Protocol:

Each eligible subject was randomly assigned to treatment or placebo group by using the random number generation function in a commercially available software program (Excel, Microsoft Inc.). Subjects in the treatment group received 0.4 % dexamethasone sodium sulfate dissolved in distilled water, whereas the placebo group received distilled water. Neither the investigators nor the subjects were aware of the treatment assignment. A staff person not involved in the study was responsible for subject randomization and prepared the solutions in identical containers which could only be differentiated by the group label.

We used self-adhering buffered, 10.1 cm^2 iontophoretic electrodes with 2.5 ml fill volume (Empi Canada). The drug was applied to the delivery electrode placed over the carpal tunnel area. The return electrode was moistened with distilled water and positioned over the ventral surface of the upper forearm. Since the dexamethasone sodium sulfate solution was negatively charged, the delivery electrode was connected to the cathode and the return electrode was connected to the anode [16]. A Dupel Ionto Unit (Empi Canada, Montreal, Quebec, Canada) was used to deliver a total dose of 80 mA.min continuous DC current, at a rate of 2 mA/min for 40 minutes (Fig. 5.1). The total dose of 80 mA.min is the maximum dosage that the Ionto Unit delivers and is considered to be safe. Patients received 6 treatment sessions on alternate days over a two-week period. Subjects were requested to refrain from using any other conservative treatment during their participation in this study.

5.2.5 Outcome Measure Tools:

We used four outcome measure tools to monitor the effectiveness of treatments for six months. The first post-treatment assessment was done within 3 days after the sixth treatment session (post-Rx0), and then on a monthly basis for up to six months (post-Rx1 to post-Rx6). These outcomes were compared with the pre-treatment values (pre-Rx). Nerve conduction studies, however, were not carried out at post-Rx0 because an immediate significant change in motor and sensory values was not expected.

5.2.5.1 nerve conduction studies:

Median motor and sensory nerve conduction studies were carried out according to the same methods used for diagnosing CTS. The parameters that were used in assessments were maximal CMAP negative peak amplitude, terminal motor latency, sensory conduction velocity of action potential across the carpal tunnel and its negative peak amplitude.

5.2.5.2 Levine's Self-Assessment Questionnaire for CTS:

To assess severity of the subjective symptoms, patients were asked to complete the Levine's Self-Assessment Questionnaire for CTS symptom severity [21]. This questionnaire for CTS has been shown to be more sensitive for CTS patients than other questionnaires such as the Disabilities of the Arm, Shoulder, and Hand (DASH) questionnaire and the 36-item Short-Form Health Survey (SF-36) [22].

The Levine's Self-Assessment Questionnaire for CTS consists of two parts: 1) a symptom severity scale that comprise of 11 items scored on a Likert scale inquiring about pain, paraesthesia, numbness, weakness, nocturnal symptoms and overall functional status, and 2) a functional status scale consisting of eight questions regarding activities of daily life that are commonly affected by CTS. The symptom severity scores ranged from 1 to 5 with 1 representing no symptoms and 5, very severe symptoms. The functional status scores also ranged from 1: no difficulty to do a task, to 5: inability to do a task (Appendix 1). We used the total severity score on this questionnaire for data analysis.

5.2.5.3 The Purdue Pegboard Test:

We used the Purdue Pegboard Test to monitor the impact of treatments on manual dexterity. The Purdue Pegboard Test is a standardized hand function tool with proven validity and reliability in the functional evaluation of CTS patients [23;24].

The Purdue Pegboard Test (Model 32020, Lafayette Instrument Company, IN, USA) consists of 50 holes arranged in two parallel columns and pegs, washers, and collars located in four cups at the top of the board. The pegs are placed in cups on the far right and far left of the board that could be conveniently reached by both hands.

The pegboard was located on a table crosswise, and subjects sat comfortably in front of it. Subjects were instructed to start the test on a verbal cue, while an examiner timed the test with a stopwatch. Subjects had 30 s to fill the holes with pegs initially with the hand intended for surgery and then with the other hand. Each subset was repeated three times to obtain an average. Test scores equaled the number of filled holes which were used as the determinant of manual dexterity. The Purdue Pegboard Test has two additional subsets which are performed bimanually. However, that did not apply to this study since we intended to compare the function of the treated and non-treated hands separately.

5.2.5.4 Semmes Weinstein Monofilaments (SWM):

As sensory complaints are prominent in CTS, we used a test kit of 20 SWM (Sammons Preston Rolyan-Canada) to assess the impact of treatments on hand sensation. This tool that examines the sensation threshold has proven reliability [25] and is utilized in the clinical evaluation of peripheral nerve diseases such as diabetic neuropathy [26;27].

We employed the standard methods for SWM [28]. Briefly, subjects were asked to stabilize their hands over a table, and keep their eyes closed for the duration of this test. Each filament, starting with the thinnest caliber, was tested over the pulp of digits. The filament was applied perpendicularly for 1 to 1.5 seconds in three trials. Subjects were asked to indicate the area where the filament was felt. A positive response in at least one of the three trials marked the sensation threshold. If subjects failed to feel a filament, filaments with the next higher caliber were employed until a positive response was obtained. We tested the sensory threshold of all digits at random to make it unpredictable to subjects. For data analysis, we used the test results of the third digit where sensory nerve conduction studies were also done.

5.2.6 Statistical Analysis:

The statistical program SPSS 12.0 for Windows was used in this study. We used the Wilcoxon Signed Ranks test to compare the outcome measures within each group. Outcomes at each follow-up session were compared with the pre-treatment values. The statistical significance was set at $p<0.05$.

5.3 Results:

5.3.1 Subjects:

Twenty eligible subjects, 19 female and 1 male, participated in the study. Randomization allocated 10 subjects to each treatment group. The range of MUNE in the thenar muscle was from 126 to 515 with a median of 256, suggestive of mild to moderate severity CTS. All subjects received the allocated treatment. However, 3 female subjects, 2 in the treatment group and 1 in the control group were later excluded from the study: 2 subjects underwent carpal tunnel decompression surgery during follow-up, and the other developed tenosynovitis due to strenuous manual labor. Consequently, the results pertain to 17 subjects who completed the study.

The subjects were 36 to 73 years old, with an average age of 54±10 years (mean±SD). They represented various occupations such as housewives, nurses, medical and laboratory technicians, cooks, manual laborers, and retirees. Thirteen subjects were right handed, defined as the hand used for writing and the remaining four were left handed. Clinical investigations and nerve conduction studies confirmed bilateral CTS in all subjects. The selection of one hand for treatment was based on handedness, CTS severity, and subjective assessment of severity by patients. The dominant hand in 15 cases presented with more severe CTS and was chosen for treatment. All subjects complied with the six-month follow-up schedule, except for one subject in the treatment group due to demanding job commitments.

5.3.2 Outcomes:

5.3.2.1 nerve conduction studies:

a) median motor conduction studies:

The maximum normal limit of terminal motor latency for median nerve is 4.2 ms [17]. This parameter had a median value of 5.1 ms for the treatment group and 5.5 ms for the placebo group at baseline. There was no significant change in either group throughout the post-treatment phase ($p \geq 0.2$) (Fig. 5.2).

In the pre-treatment assessment, the CMAP amplitude was in the normal range, with a median of 7.7 mV for the treatment group and 8.5 mV for the placebo group. The CMAP amplitude remained the same throughout the study ($p \geq 0.1$). While the placebo group also did not change following treatment in post-Rx1 and post-Rx2 ($p \geq 0.05$), there was a significant worsening in the CMAP amplitude at post-Rx 3 ($p=0.02$) which later resolved (Fig. 5.2).

b) median sensory conduction studies:

The minimum cut off for normal median sensory conduction velocity across the carpal tunnel was 50 m/s [17]. This velocity had a median of 25 and 30 m/s for the treatment and placebo group respectively. None of the treatments accelerated the transcarpal sensory conduction velocity ($p \geq 0.1$) (Fig. 5.3).

In healthy subjects, the negative peak amplitude of sensory nerve action potential (SNAP) of median nerve is at least 20 μV. The median SNAP amplitude was less than 12 μA for both groups prior to treatment. It did not improve in either group ($p \geq 0.1$)(Fig. 5.3).

5.3.2.2 Levine's Self-Assessment Questionnaire:

The score for a healthy subject with no hand symptom on the Levine's Self-Assessment Questionnaire is 19. As the severity of CTS increases, Levine's symptom severity score also increases. The maximum score is 95 in very severe cases.

In this study, the total subjective severity score ranged from 21 to 60, with a median of 38 and 36 for the treatment and placebo group respectively (Fig. 5.4). Subjects in the treatment group reported a significant improvement of symptoms by post-Rx5 and 6 ($p<0.05$), and achieved a median score of 25 by post-Rx6. Those in the placebo group also reported a significant reduction in symptoms by post-Rx4 ($p=0.012$) and post-Rx6 ($p=0.028$), and reached a median score as low as 30. None of the subjects in either group reported to be symptom free at any point after the treatment.

5.3.2.3 The Purdue Pegboard Test:

The Purdue pegboard Test determines the manual dexterity of the subjects as reflected by the number of holes they could fill in 30 s. As the manual dexterity declines, subjects score less on the number of holes that could be filled. The average normal score is 17 with an overall range of 13 to 19 pegs [23].

The median number of pegs manipulated by subjects before treatment was 13 for both groups. This test did not detect any significant change on the manual dexterity of the treatment group ($p \geq 0.06$); the median score for this group reached 14 pegs by post-Rx6 (Fig. 5.5). In contrast, the hand function of subjects in the placebo group had significantly improved at post-Rx6 ($P < 0.05$). To determine whether this finding could be due to practice effect, the non-treated hand was assessed too. Interestingly, the non-treated hand also improved, suggesting that practice effect was a likely possibility ($p < 0.05$).

5.3.2.4 Semmes Weinstein Monofilaments:

Each monofilament of the Semmes Weinstein kit is calibrated to apply a certain pressure per cm^2 surface area of the skin. The first 4 filaments represent the normal threshold of sensory perception (4.5—67.7 mg/cm^2), filaments 5 and 6 represent diminished light touch (166—408.2 mg/cm^2), and filaments 7 to 10 represent diminished protective sensation (695.8—2052 mg/cm^2). The last 10 filaments mark the loss of protective sensation (3632—447000 mg/cm^2).

At baseline, subjects in both groups had a median sensory threshold of 27 mg/cm^2, which was within the normal range. This is perhaps not surprising since the patients recruited in this study only had mild to moderate CTS. The sensory threshold did not further improve in either group following treatment ($p \geq 0.1$) (Fig. 5.6).

5.4 Discussion:

Transcutaneous delivery of corticosteroids using iontophoresis is a potentially appealing alternative to intracarpal injection of corticosteroids. This is the first controlled study that evaluated the effects of corticosteroid iontophoresis to treat mild to moderate CTS.

Findings in the present study did not support the effectiveness of dexamethasone iontophoresis in treating CTS. The only outcome measure that showed significant improvement following corticosteroid iontophoresis was the subjective symptom severity score on Levine's Self-Assessment Questionnaire. This improvement was noticed 5 and 6 months after the treatment. However, the same improvement was also reported by the control group suggesting that such subjective measures likely have a strong placebo effect. We did not detect any improvement in the manual dexterity of the subjects in the treatment group. Interestingly, manual dexterity of the placebo group did improve in the control group. However, the same was also noted even in the non-treated hand of the control group, indicating that this finding was perhaps due to practice. We believe that the deterioration in the CMAP amplitude of the control group at post-Rx3 is not of clinical significance, since it was not a consistent finding throughout the follow-ups.

To our knowledge, only two other studies have used corticosteroid iontophoresis to treat CTS. Although both studies had concluded a positive effect, each had limitations. In the first study, 23 hands were treated with wrist splints and ibuprofen for 3 weeks. Subjects who were non-responsive to this treatment (83%) were treated with corticosteroid iontophoresis for 3 sessions over one week, while using the wrist splint simultaneously. The rate of success was reported to be 58%, determined by normalization of nerve conduction studies and near complete recovery of symptoms [29]. In addition to being non-randomized and unblinded, this study had studied the response to therapy while subjects were using two treatments simultaneously. Therefore, it is difficult to firmly attribute the positive effect to corticosteroid iontophoresis.

The second study compared the effectiveness of corticosteroid injection with that of corticosteroid iontophoresis for 3 sessions, in 48 hands [30]. The authors detected a positive effect for both treatments up to 8 weeks, with the outcome of corticosteroid injection being superior to iontophoresis. Unfortunately, the only outcome measure used by these investigators was subjective functional and symptom severity scores. Although in our study we also detected a significant improvement based on the subjective symptom severity scores, this effect was also noted in the placebo group. This discrepancy suggests that having a placebo control group is crucial.

What are the potential reasons for the negative findings in this study? One possibility is that the dose of corticosteroid administered was insufficient compared to the injection method. However, we feel that is unlikely for several reasons. First, the dose regime that we chose was the same as those administered by other investigators [29;30;32]. Second, that dosage was also recommended by the manufacturer of the iontophoresis unit. The total dose of 60 mg dexamethasone was delivered over 6 sessions was substantially higher than the dosage of corticosteroid used for injection. Twenty mg of injected methylprednisolone has been reported with positive effect [31].

A separate issue is whether sufficient amount of dexamethasone penetrated through to the carpal tunnel. Glass et al., by administering radioactively labeled dexamethasone in rhesus monkeys, has shown that iontophoresis is capable of delivering the medication as deep as 17 millimeters from the surface of the skin [33]. Also in rhesus monkeys, Anderson et al. showed that cathodal iontophoresis of dexamethasone at 40 mA.min dosage delivers the medication to a depth of 12 mm in agarose gel [34]. Studies on the rhesus monkey demonstrated that skin underneath the iontophoresis electrode contained the highest concentration of dexamethasone after iontophoresis, and tissues deeper than 3 mm received less than 10% of the medication. Likewise, Anderson et al. showed that diffusion delivered less than 10% of the dexamethasone to more than 8 mm depths of the agarose gel. Although the quantity of iontophoresized corticosteroids reaching various tissue depths has never been measured in humans, insufficient amount of dexamethasone penetration to the carpal tunnel remains a potential explanation for the negative results found in this study.

One may speculate that increasing the magnitude of current from 2 mA/min to 4 mA/min might have shown a positive effect. However, this possibility is unlikely based on the work of Anderson et al. They showed that the effectiveness of dexamethasone delivery, as indicated by constriction of the cutaneous vasculature, was in fact longer lasting and greater in magnitude when using low-current, long-duration of iontophoresis rather than high-current, short-duration treatment [34].

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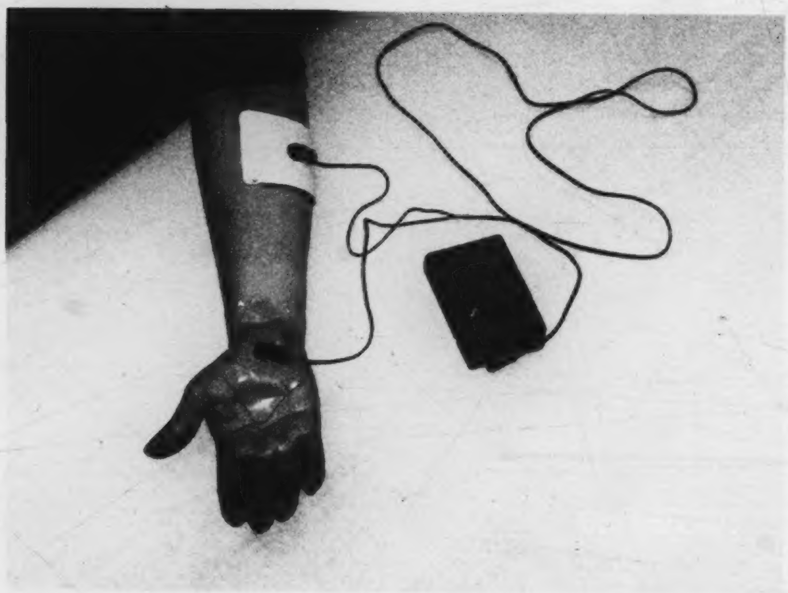


Figure 5.1. The experiment set up.
The cathodic pole of the Ionto Unit is connected to the treatment electrode over the carpal tunnel area, and the anodic pole is connected to the return electrode over the forearm.

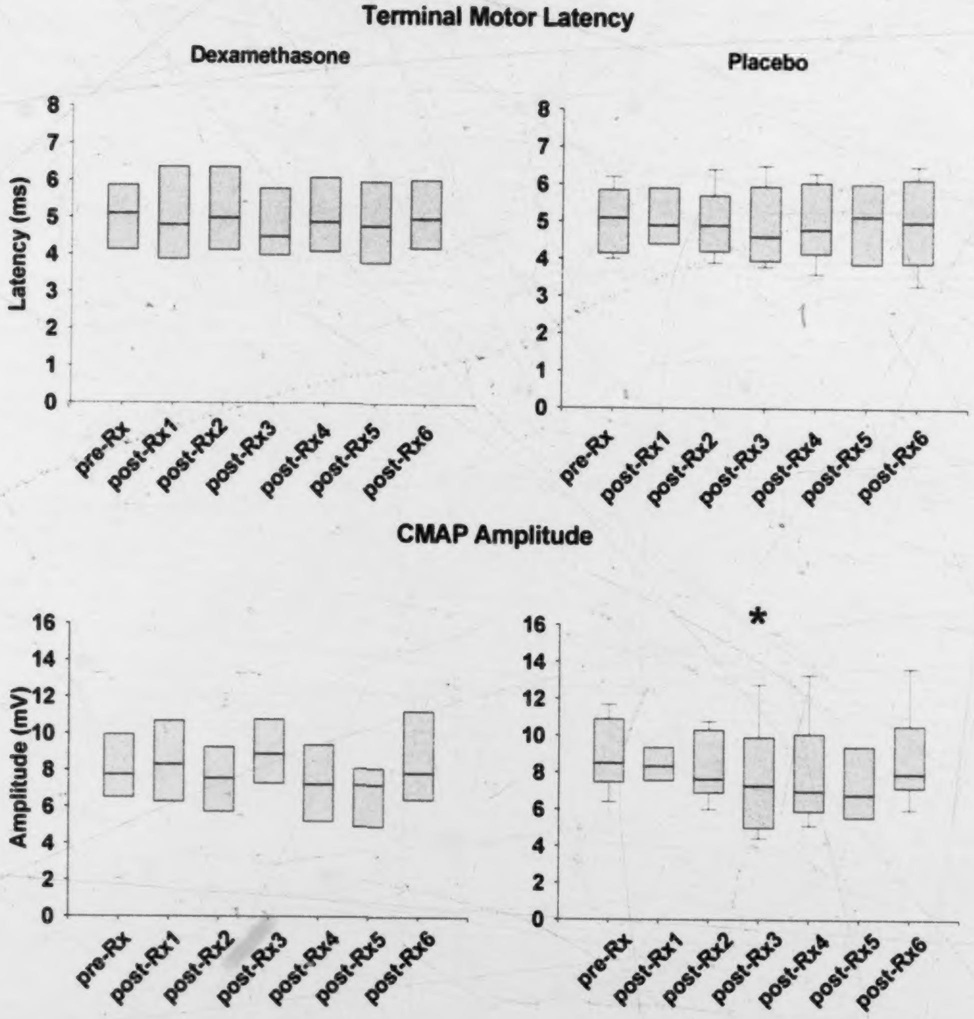


Figure 5.2. Results of motor nerve conduction studies
Box plots represent median (middle line), 75th and 25th percentiles (upper and lower margins of the box plots) 90th and 10th percentiles (upper and lower whiskers respectively). Absence of whiskers denotes that results were within the 25th and 75th percentile range. * denotes $p<0.05$.

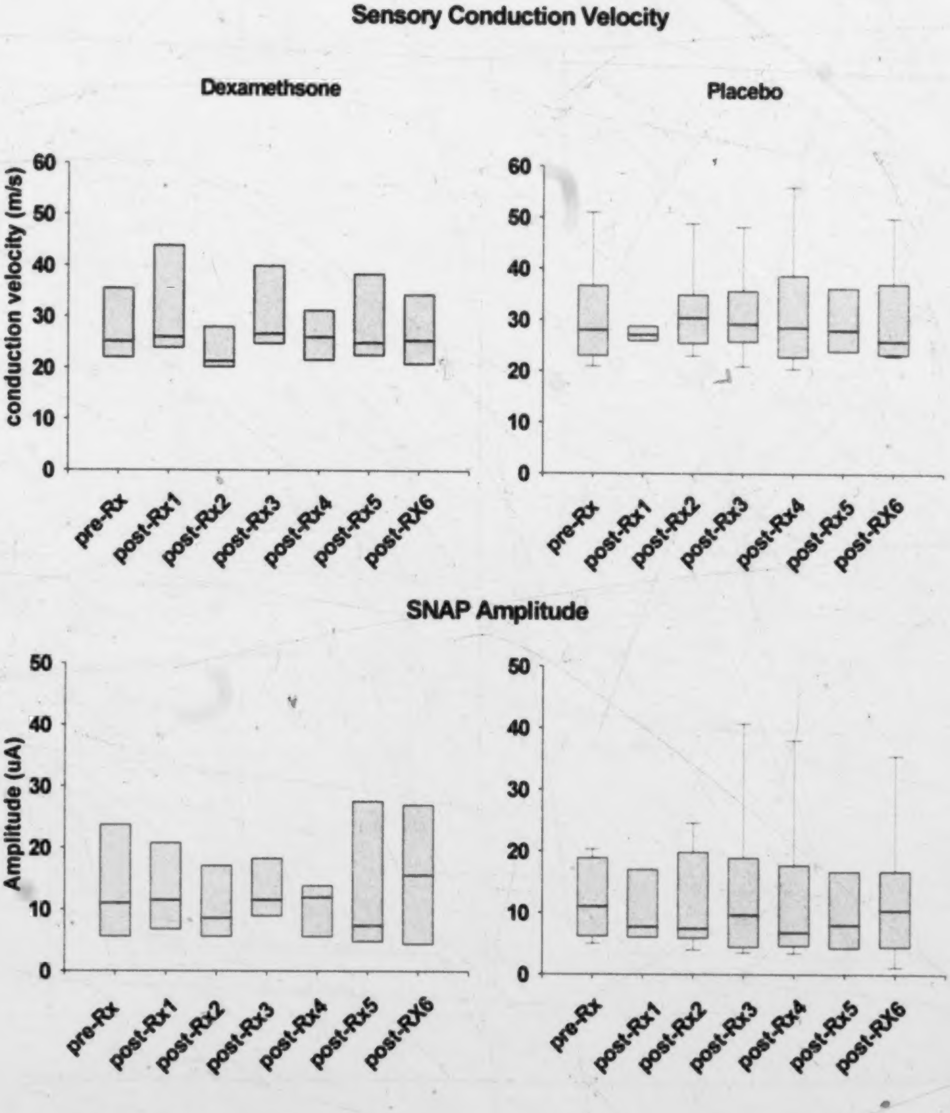


Figure 5.3. Results of sensory nerve conduction studies.
Box plots represent median (middle line), 75th and 25th percentiles (upper and lower margins of the box plot), 90th and 10th percentiles (upper and lower whiskers respectively). Absence of whiskers denotes that results were within the 25th and 75th percentile range.* denotes $p<0.05$.

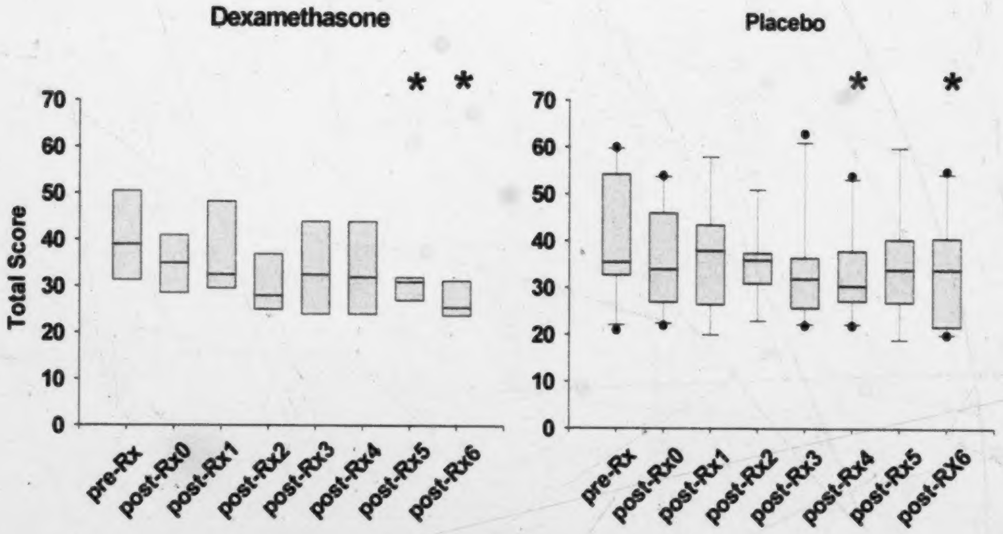
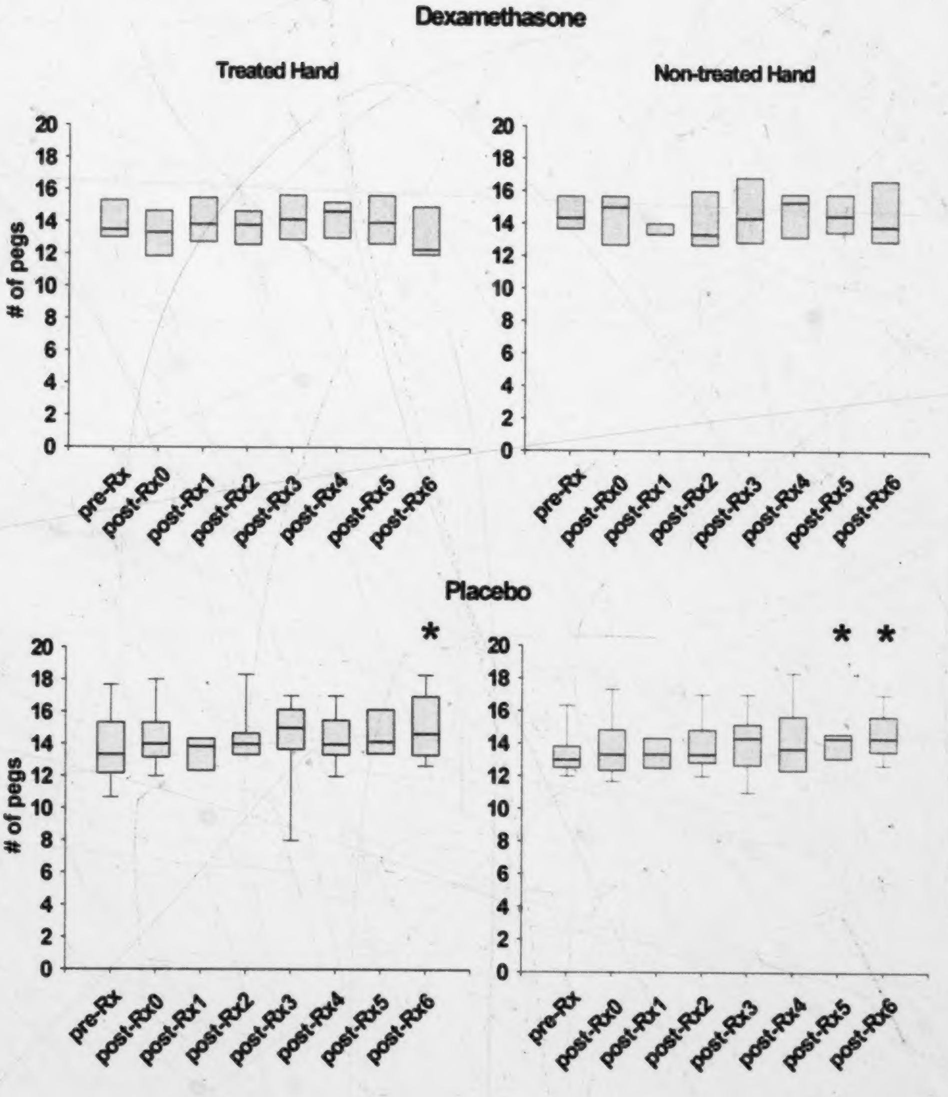


Figure 5.4. Results of Levine's Self-Assessment Questionnaire.
Box plots represent median (middle line), 75th and 25th percentiles (upper and lower margins of the box plots), 90th and 10th percentiles (upper and lower whiskers respectively). Absence of whiskers denotes that results were within the 25th and 75th percentile range. Black dots present the entire range. * denotes $p<0.05$.


Dexamethasone

Treated Hand

Non-treated Hand

Placebo

Figure 5.5. Results of the Purdue Pegboard Test.
Box plots represent the median (middle line), 75th and 25th percentiles (upper and lower margins of the box plots), 90th and 10th percentile (upper and lower whiskers respectively). Absence of the whiskers denotes that all the data were within the 25th and 75th percentile range. When median is absent, it has overlapped the 25th percentile.* denotes $p<0.05$.

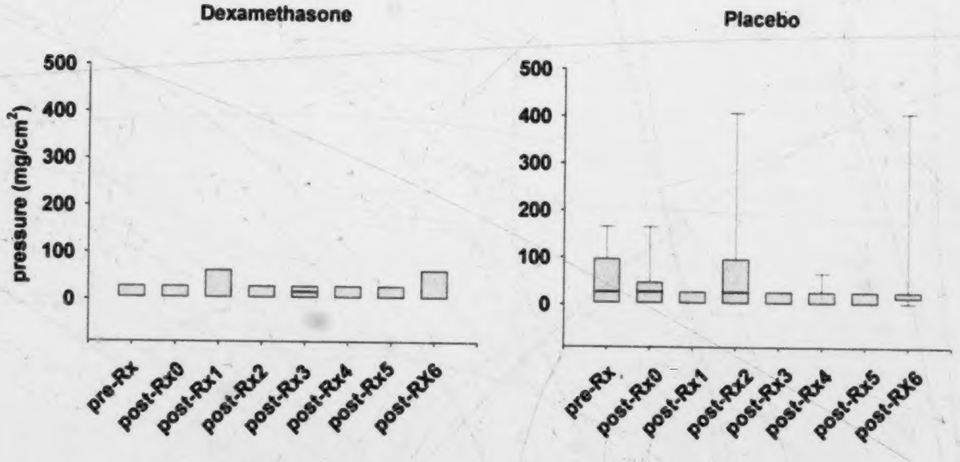


Figure 5.6. Results of Semmes Weinstein Monofilaments.
Box plots represent median (middle line), 75th and 25th percentiles (upper and lower margins of the box plot), 90th and 10th percentiles (upper and lower whiskers respectively). Absence of whiskers denotes that results were within the 25th and 75th percentile range. When middle line is absent it has overlapped with the 25th or the75th percentile.

Chapter 6

6.0 General Discussion and future directions:

The prevalence of clinically and electrophysiologically confirmed CTS in the general population of the United States is 2.7% [1]. This translates to approximately 8 millions affected individuals. These patients constitute a large number of neurology, physiatry, rheumatology, and orthopedic visits. Despite such high prevalence, treatment options are fairly limited and therefore investigations of novel treatments are much needed. In addition, CTS also serves as a useful model to study compression nerve injuries in humans. Therefore, in this thesis, we carried out four projects on CTS. The first and second projects addressed functional issues attributed to the median nerve entrapment. The third and fourth projects were designed to study practical treatment options for severe as well as milder forms of CTS.

6.1 Project 1: establishment of norms for the Moberg Pick-Up Test:

Although there are a number of tests available in the literature for evaluating hand functions, few are designed for measuring fine manual dexterity. For instance, dynamometers are used only for measuring the grip strength [2;3], whereas the Jebsen Taylor Test only measures gross hand function such as the gripping of large objects [4]. In contrast, the Moberg Pick-Up Test is suited for assessing fine manual dexterity by engaging the median innervated territory of the hand [5]. In the first project, we established age specific norms for the Moberg Pick-Up Test by studying 116 subjects. This is the largest sample of subjects that has ever performed the Moberg Pick-Up Test. Such a large sample size makes it feasible to study other influencing factors such as age and gender. The results confirmed deterioration of hand function with age and women had faster hand function than men. These are important factors that need to be taken into account as CTS affects a wide range of individuals.

Although there were fewer male participants in this study especially in the elderly group, this did not pose a problem since the sample had sufficient power to detect a significant difference between the genders, a finding which concurs with that of other investigators [6]. Our results showed that age, gender and handedness affect the test, with young subjects being faster than the elderly, females faster than males, and the dominant hand faster than the non-dominant hand.

The goal of this project was to provide a comprehensive set of normative values that can be used in clinical settings for evaluation of hand disability and the effectiveness of rehabilitation. Since treatment and rehabilitation can be a lengthy process, test-retest reliability of the Moberg Pick-Up Test needs to be addressed. Inter rater reliability of this tool was examined by Ng et al. on only 14 subjects [6]. This small sample was not sufficiently powered to demonstrate the test-retest reliability of the test. Also, patients may demonstrate a significant improvement in their manual dexterity simply due to multiple repeats of the test. Therefore, further investigations to demonstrate whether practicing and learning influences the results need to be carried out. Additionally, the inter tester reliability of the Moberg Pick-Up Test has never been investigated. This is an important consideration because in longitudinal follow-up of patients, it is likely that more than one practitioner will be involved.

6.2 Project 2: validity and reliability of the Purdue pegboard Test and the Moberg Pick-Up Test in CTS

Many CTS patients fail to resume work, even after carpal tunnel decompression surgery, suggesting that their hand function may still be impaired [7]. Yet, subjective symptom severity questionnaires and nerve conduction studies remain as the most common evaluation tools [8-10]. This is in part because of a lack of valid and reliable hand function test applicable to these patients. The second project was aimed at examining the validity and reliability of the Purdue Pegboard Test and the Moberg Pick-Up Test in CTS patients. We studied a large sample of 123 control and 115 CTS subjects, which permitted age-matched comparison.

The gender mix in the control and patient groups was similar. The results showed that the Purdue Pegboard Test and the Moberg Pick-Up Test both showed significant functional difference between healthy age matched controls and CTS patients. We classified patients with different severities of CTS using two commonly used methods: nerve conduction studies [11] and the Levine's Self-Assessment Questionnaire [12]. We noticed that both methods of defining the severity of CTS posed discrepancies. For instance middle aged subjects with moderate CTS based on nerve conduction values performed all subsets of the Moberg Pick-Up Test faster than mild cases. One reason is that these criteria measure different aspects of the median nerve functions. Indeed, table 3.1 clearly shows that the two methods have low concordance with each other even within the same subject.

Both dexterity tests proved to be highly reliable in CTS when 32 subjects repeated the tests for a second time. Furthermore, performance of subjects on both tests was significantly correlated, suggesting that either test can be used in a clinical setting.

A limitation of our study was that healthy subjects were not examined by nerve conduction studies and the Levine's Self-Assessment Questionnaire. This could be particularly important in the elderly group when the mild CTS patients were faster on both dexterity tests than the healthy control. One possibility is that some asymptomatic elderly subjects may in fact have mild forms of median nerve compression on nerve conduction studies or the symptom questionnaire. However, these tests were not done in the healthy subjects and will need to be further investigated.

6.3 Project 3: enhancement of axonal regeneration after decompression of the median nerve by using the electrical stimulation

Compression neuropathies are common in humans [13]. In advanced cases, marked axonal degeneration can occur, leading to functional limitations [14]. Unfortunately, translation of strategies promoting nerve regeneration still largely remains in the domain of animal studies where noticeable advances have occurred. The third project of this thesis was the first attempt to extend the application of electrical stimulation to augment nerve regeneration [15] to humans.

The third project proved that 1-hour electrical stimulation enhances the regeneration of median nerve axons. Equally important was that we demonstrated the electrical stimulation is feasible and applicable to human subjects too. Subjects tolerated the procedure well since the hand was already anesthetized during the OCTR. Furthermore, insertion of wire electrodes over the median nerve only prolonged the OCTR for a few more minutes.

To further improve the applicability of this method in clinical settings, it would be interesting to explore whether the duration of stimulation could be further reduced. Since the dexterity and sensory test did not discriminate the impact of electrical stimulation compared to controls, other functional tests such as grip, and pinch strength as well as physiologic outcome measures such as maximum voluntary contraction, and muscle tetanic tension may be worth pursuing in future studies. This may provide important information since the significant improvement in the MUNE noted in the stimulation group indicates effective nerve-muscle connection of the motor axons in addition to their re-growth [16].

This study did not provide any information about the physiologic mechanism by which electrical stimulation enhanced axonal regeneration. Based on evidence in the literature, we suspect that this effect is controlled by the cell body of the motoneurons [15]. Other investigators showed that electrical stimulation increases the expression of mRNA of substrates that are associated with axonal regeneration. These included BDNF, Tα1-tubulin, and GAP 43 [17;18]. Although molecular studies are not feasible on intact humans, it is possible to study the role of retrograde propagation of the stimulation volley along the median nerve by blocking it at a more proximal location from the stimulation site, such as the elbow, using a local anesthetic agent such as lidocaine.

In this study, electrical stimulation was effective when applied to the proximal edge of the nerve compression site. Further studies are required to investigate whether stimulating the nerve at a proximal site such as the elbow would exert the same effect. The stimulation can be administered through an EMG needle at a proximal location in the arm. If proven to be effective, proximal median nerve stimulation will eliminate the need for intra operative insertion of wire electrodes during carpal tunnel decompression surgery.

It is possible that electrical stimulation may also have the same effect in other forms of nerve entrapments. If that is true, it may be particularly critical in situations where the length of regeneration is longer. In those cases, the time for the sprouting nerve fibers to reach the target muscles become critical. An example is ulnar nerve compression at the elbow. The ulnar nerve is responsible for innervation of many of the hand muscles, especially two muscles in the thenar eminence and two of the lumbrical muscles. Currently, the outcome of ulnar nerve decompression surgery is considerably poorer than that of carpal tunnel decompression.

6.4 Project 4: ineffectiveness of corticosteroid iontophoresis in treating mild and moderate CTS

Patients with mild to moderate CTS are often reluctant to undergo carpal tunnel decompression surgery. However, conservative treatments for CTS with proven benefits are limited [19]. Although injection of corticosteroids into the carpal tunnel is considered a conservative treatment, it is not without risk and is painful [20].

The last project was designed to investigate delivery of the medication through the skin by using the method of iontophoresis.

While symptoms in the treated patients improved, those in the control group also improved and there was significant difference between them. This observation points to the importance of using a double-blind randomized controlled design as subjective perceptions can easily color treatment outcomes. Therefore, we could confidently conclude that iontophoresis of 0.4% dexamethasone does not bring about any relief to CTS, although subjects reported reduction of their symptoms over the course of six months. This improvement was noted in both the treatment and the placebo group. Without blinding and randomized controls, previous studies were misled about the effectiveness of dexamethasone iontophoresis [21;22]. Based on the uncontrolled data, corticosteroid iontophoresis was suggested to be an effective treatment for CTS.

One of the limitations of this study was that the sample size was relatively small. That was in part due to the stringent inclusion and exclusion criteria. However, based on the results, we do not believe that increasing the sample size would lead to a different conclusion. First, all the outcome measures were consistent over six months of follow-up in the treatment group. Furthermore, the improvement in dexterity detected in this study belonged to the control group but not the treatment group.

This study clearly demonstrated that Semmes Weinstein Monofilaments, which are commonly used to examine sensation changes in CTS, did not discriminate the sensory abnormalities in mild and moderate subjects at baseline. This finding implies that Semmes Weinstein Monofilaments may have limited usage in the assessment of CTS depending on the severity of the ailment. This possibility has never been investigated, but warrants further studies.

The concentration of dexamethasone used in this project was 0.4% which is commonly used in the literature [21;23]. A total dose of 60 mg dexamethasone was delivered during six sessions. Increasing the concentration of dexamethasone is unlikely to demonstrate a positive therapeutic effect.

6.5 Concluding remarks:

The work in this thesis shows that CTS impairs hand function even in mildly affected subjects, which can be validly and reliably quantified by the Purdue Pegboard test and the Moberg Pick-Up Test. However, these dexterity tests are affected by the age, gender and handedness of subjects. This was already shown in case of the Purdue Pegboard Test, and we demonstrated the same trend for the Moberg Pick-Up Test in this thesis. One-hour electrical stimulation of the median nerve after OCTR augments the axonal regeneration in the severe CTS cases that have undergone axonotmesis. Corticosteroid iontophoresis does not relieve CTS symptoms even in mild and moderate cases.

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Appendix 1:

Levine's Self-Assessment Questionnaire for Carpal Tunnel Syndrome

Subject ID# ____________________ **Date** __________

The following questions refer to your symptoms for a typical twenty-four (24) hour period during the past two weeks (circle one answer to each question).

A. How severe is the hand or wrist pain that you have at night?

1. I do not have hand or wrist pain at night.
2. Mild pain
3. Moderate pain
4. Severe pain
5. Very severe pain

B. How often did hand or wrist pain wake you up during a typical night in the past two (2) weeks?

1. Never
2. Once
3. Two or three times
4. Four or five times
5. More than five times

C. Do you typically have pain in your hand or wrist during the daytime?

1. I never have pain during the day
2. I have mild pain during the day
3. I have moderate pain during the day
4. I have severe pain during the day
5. I have very severe pain during the day

D. How often do you have hand or wrist pain during the daytime?

1. Never
2. Once or twice a day
3. Three to five times a day
4. More than five times a day
5. The pain is constant

E. How long, on average, does an episode of pain last during the daytime?

1. I never get pain during the day
2. Less than 10 minutes
3. 10 to 60 minutes
4. Greater than 60 minutes
5. The pain is constant throughout the day

F. Do you have numbness (loss of sensation) in your hand?

1. No
2. I have mild numbness
3. I have moderate numbness
4. I have severe numbness
5. I have very severe numbness

G. Do you have weakness in your hand or wrist?

1. No weakness
2. Mild weakness
3. Moderate weakness
4. Severe weakness
5. Very severe weakness

H. Do you have tingling sensation in your hand?

1. No tingling
2. Mild tingling
3. Moderate tingling
4. Severe tingling
5. Very severe tingling

I. How severe is numbness (loss of sensation) or tingling at night?

1. I have no numbness or tingling at night
2. Mild
3. Moderate
4. Severe
5. Very severe

J. How often did hand numbness or tingling wake you up during a typical night during the past two (2) weeks?

1. Never
2. Once
3. Two or three times

4. Four or five times
5. More than five times

K. Do you have difficulty with the grasping and use of objects such as keys or pens?

1. No difficulty
2. Mild difficulty
3. Moderate difficulty
4. Severe difficulty
5. Very severe difficulty

Functional Status Scale

On a typical day during the past two weeks have hand and wrist symptoms caused you to have any difficulty doing activities listed below? Please circle the one number that best describes your ability to do the activity.

Activity	No Difficulty	Mild Difficulty	Moderate Difficulty	Severe Difficulty	Cannot do at all due to hand or wrist symptoms
Writing	1	2	3	4	5
Buttoning of clothes	1	2	3	4	5
Holding a book while reading	1	2	3	4	5
Gripping of a telephone handle	1	2	3	4	5
Opening of jars	1	2	3	4	5
Household chores	1	2	3	4	5
Carrying of Grocery Bags	1	2	3	4	5
Bath and dressing	1	2	3	4	5